Durable memories are not underpinned by stronger activations in encoding networks

An event-related fMRI study

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Abstract

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Supervisor: Markus H. Sneve / **Co-supervisor**: Anders M. Fjell

Background: Our brain's potential to develop and reference long-lasting durable memories is an essential contributor to human evolutionary success. Of the multitude of experiences we encounter each day, only a very small subset go on to develop memory representations that are recallable after a delay period of weeks or months. However, little is known about whether or not neural mechanisms under the initial encoding of events potentially govern the selection of memories that will become subject to systems consolidation processes, and consequently durable. **Aim**: The aim of the present study was to put two accounts of durable memory formation to the test, and to replicate and extend the results of a recent between-groups investigation in a within-groups sample. **Method**: A rapid event-related fMRI design was employed; 26 subjects were scanned whilst encoding 200 item-action evaluations and tested for later memory at two separate timepoints: both ~1.5 hours and ~3 weeks later. **Contributions**: The experiment was part of a larger project within the Research Group for Lifespan Changes in Brain and Cognition, and the author was involved in the design, programming, and undertook all of the data collection. The analysis was carried out independently using a combination of self-written and pre-written scripts. **Results**: Greater recruitment of hippocampus and distributed cortical episodic encoding networks predicted the formation of recollection memories tested after 1.5 hours, relative to both subsequently forgotten events and events remembered by weaker, more familiarity-based processes. In contrast, the encoding of durable memories was not underpinned by stronger recruitment in hippocampus, nor in typical episodic-related cortical structures, at least not beyond that which was necessary for successful representation in memory across a short delay. Moreover, this held for both durable recollection and durable recognition memory. Results indicate that the intensity-dependent account for memory formation was only apparent for memories that lasted a short duration, and that a critical threshold must be surpassed for a memory to potentially become durable, but that this threshold may be common both to the encoding of memories that last a short-delay, and those that go on to become more robustly represented in time. **Conclusion**: It is concluded that the selection of memories to undergo further post-encoding consolidation does not seem to be governed by processes that reflect the level of engagement of neural networks under encoding.

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Now to the pub!

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1. Introduction

The vast majority of information that we encounter on any given day does not become consciously recallable in memory. Following the encoding of events, much of our initial memory traces will be forgotten, whereas for other traces in memory, the ability to recall detailed recollections surrounding events erodes over time. For a select few, however, detailed representation over longer periods of time is made possible. Even when encoding conditions apparently remain constant, some memories endure longer than others. Our understanding as to why some memories persist over others in the weeks following an experience is far from complete, because research investigating the brain mechanisms evident during encoding that amount to memory-longevity is very much lacking. Specifically, what (if any) neural mechanisms under the initial encoding of an experience can predict the durability of episodic experiences over time?

Inherent to the self-construct is the notion that we are an entity that exists within time and space with an accumulated personal history of experiences. In psychological terms, this is known as one's episodic memory, and it refers to the conscious process of internally re-experiencing previously lived out events in order to recount them externally. However, it is a common observation in many aspects of psychology that the accuracy of such recounted episodes is commonly overstated by the experiencer (Smith, Kassin, & Ellsworth, 1989; Sporer, Penrod, Read, & Cutler, 1995). Because the details of memory are prone to error and distortion from both internal and external sources, it is now accepted that episodic memory is a primarily reconstructive phenomenon, as opposed to a reproductive one (Schacter & Addis, 2007). In addition, for survival across time, an episodic memory has to be supported by neural processes at all stages in the memory lifecycle, including under encoding, consolidation and retrieval. Thus, the complexity of the re-creative nature of memory is further compounded by brain processes that serve to keep a memory alive, as this requires neural resources that amount to the effective maintenance of memories within the brain.

Every hour consists of a multitude of events, only some of which will go on to gain the neural real estate required for effective retrieval in the short-term, and even less will survive as durable representations in time. Doubtlessly, both episodic memory accuracy (Schmolck, Buffalo, & Squire, 2000) and its neural representation (Viskontas, Carr, Engel, & Knowlton, 2009) decline as a function of time. To achieve stable representation across time then, it is believed that a memory must consolidate and either integrate into existing memory networks, stabilise as its own, or else risk losing neural representation altogether, becoming consequently forgotten (Stickgold & Walker, 2013). However, very little research has been

conducted to investigate the neural mechanisms during the encoding of events that subsequently leads to the development of the most durable memory representations.

1.1. Encoding-related Neural Activity: Short-duration Memory

Perhaps unsurprisingly, neural activity elicited under the encoding of stimuli is well established as a significant predictor of subsequent memory performance after a short delay of minutes to hours. A meta-analysis of 74 subsequent memory studies identified that successful encoding most commonly associated with an overlap of five neural regions: bilateral hippocampus, fusiform cortex, premotor cortex, posterior parietal cortex (PPC), and left inferior frontal gyrus (IFG) (Kim, 2011). Thus, an extensive neural network spanning memory, perceptual and attentional regions has been implicated in the successful encoding of objects leading to retention after a short delay (note, however, that a short delay of minutes to hours still falls within the traditional classification of long-term memory (Shiffrin & Atkinson, 1969, but for an updated classification, see Nadel & Hardt, 2011)).

Seminal models of memory propose that a critical role of the hippocampus is to bind the features of an experience in memory. That is, successful episodic encoding is supported by interactions between hippocampus and cortical regions that support the online perceptual processing of an event at initial exposure (Cansino, Maquet, Dolan, & Rugg, 2002; Uncapher, Otten, & Rugg, 2006). These cortical regions have been characterized into three broad groups (Kim, 2011): those involved with the processing of content that mediate a perceptual experience's transition to a memory representation (particularly left IFG and fusiform cortex), those associated with reflecting an attentional bias during encoding (such as the PPC (Uncapher & Wagner, 2009)), and those reflecting memory storage processes, of which hippocampal and medial temporal lobe (MTL) binding functions are pivotal for establishing memory traces available for subsequent conscious recollection (Hannula & Ranganath, 2008). Along these lines, it has been shown that hippocampal activity becomes increased for items that are later recollected with source memory - or memory also for the contextual features of an experience - relative to forgotten items. However, this is not the case for items recognised with a sense of familiarity, characterised by successful recognition in the absence of detailed contextual retrieval (Davachi, Mitchell, & Wagner, 2003; Diana, Yonelinas, & Ranganath, 2007). This implies that hippocampal activity under encoding exhibits an intensity-dependent relationship with the quality and depth of the subsequent memory. Moreover, greater hippocampal involvement in recollection memory indicates that hippocampus is recruited preferentially under conditions of associative encoding, as this

requires the binding of constituent perceptual features into a coherent memory representation (Davachi et al., 2003). Taken together, consistent functional magnetic resonance imaging (fMRI) evidence indicates that neural activity elicited under the presentation of stimuli is associated with successful episodic encoding for memories recounted over short intervals. Therefore, the relationship between a memory surviving a short retention period and neural activity in encoding-related brain regions seems to be positively intensity-dependent, whereby higher levels of encoding activity predict memory retention after a short delay.

Conversely, a subset of cortical regions that comprise the so-called default-mode network (DMN) show consistent deactivations during successful memory encoding (Daselaar, Prince, & Cabeza, 2004). The DMN becomes preferentially active when an individual's focus is not directed towards the external environment, but rather centers on introspective processes related to the internal narrative, including introspection, theory of mind (Buckner, Andrews-Hanna, & Schacter, 2008; Spreng, Mar, & Kim, 2009), and 'task unrelated thoughts' (Maillet & Rajah, 2013). Consistent fMRI results showing the DMN's relation to the self have recently been buttressed by single cell-recordings, confirming the selective recruitment of neurons in the human PPC – a hub of the DMN - during the processing of self-relevant information (Lipsman et al., 2014). The DMN shows an anti-correlation with task-positive networks; high metabolic activity is observed when not engaged in a task, and decreased metabolic activity is observed when cognitively focused (Raichle et al., 2001). As a consequence, Kim's (2011) meta-analysis found that positive activation in DMN structures, (including the posterior cingulate cortex (PCC), precuneus, anterior cingulate (ACC) and ventromedial prefrontal cortex (vmPFC)) is predictive of episodic encoding failure, namely interpreting higher DMN activity as related to 'mind wandering', or a lack of focus on task. In support of this interpretation, posterior midline regions have been shown to demonstrate a 'flip' in activity between successful memory encoding and successful retrieval relative to encoding and retrieval misses, respectively; DMN engagement on the whole seems most facilitative towards episodic recall, whereas DMN disengagement on the whole seems more facilitative in episodic encoding (Daselaar et al., 2009; Huijbers et al., 2012; Vannini et al., 2011). However, recent research indicates that DMN-related activity could be facilitative towards episodic memory formation (Sneve et al., 2015), and that this may depend on whether self-referential encoding strategies are used (Maillet & Rajah, 2013). As such, conflicting results as to whether DMN activity (or less deactivity) confers an advantage during episodic encoding may be somewhat reconciled with the claim that the network is commonly engaged during conditions of self-projection

(Buckner & Carroll, 2007), and self-referential thought (D'Argembeau et al., 2005). Therefore a self-projective state could either reflect a lack of engagement in the task at hand (Kim, 2011), or conversely may reflect a beneficial strategy of self-referential encoding (Maillet & Rajah, 2013), an advantageous strategy for which there is overwhelming psychological evidence for (Symons & Johnson, 1997)).

Whether a memory trace becomes strong enough to survive a short-term interval of minutes to hours depends, then, on both higher levels of encoding activity in memory relevant-networks, and lower levels of encoding activity in networks that (more often) tend to reflect task disengagement when active (Kim, 2011; Uncapher & Wagner, 2009).

1.2. Previous Durable Memory Research

Owing to the fact that the vast majority of fMRI research has tested participant memory after delays of minutes to hours, much less is known about the brain mechanisms under encoding that lead to the formation of memories that stand the test of time in the weeks following. Importantly, the development of a detailed short-duration memory representation (the neural mechanisms of which were discussed above) is a necessity for a detailed memory to persist over time (Carr, Viskontas, Engel, Knowlton, & Carr, 2010; Liu, Dong, Chen, & Xue, 2013). Therefore, only events that one can successfully recollect after a short-delay will be recalled with recollection memory after a long-delay. This, taken together with the fact that stronger encoding activity in cortical and subcortical memory networks is a prerequisite for successful recollection across a short delay (Davachi et al., 2003; Kim, 2011), indicates that the first mechanism by which durable memories are formed must also follow a principle of encoding intensity. What remains to be elucidated, however, is what pushes memories that surpass this initial encoding intensity threshold further towards a more durable representation in time.

One possibility is that the neural activity elicited under encoding simply differs on an intensity basis for memories that achieve more durable status, such that these are encoded more strongly and completely. In memory studies, high levels of fMRI-measured activity under encoding are believed to reflect rapid synaptic consolidation processes. Of the limited studies that tested subsequent memory after prolonged delays, the evidence is in support of this intensity-dependent account. When testing participants for memory for a word list, Uncapher and Rugg (2005) found that greater blood-oxygen-level-dependent (BOLD) activity in left IFG was associated with later recollection after 48 hours than after 30 minutes, indicating that additional processing here was determinative of subsequent memory durability

over at least a period of 48 hours. Similarly, activation intensity in hippocampus and underlying perirhinal cortex has previously been found to be predictive of memory durability across a period of one week (Carr et al., 2010). Another study found that durable memory for words tested after a one week delay was accompanied by decreased deactivation in the PCC during encoding, and stronger activity in the left IFG (Liu et al., 2013). Thus a simple premise of intensity-dependent neural encoding activity that predicts the endurance of episodic representations in structures known to underpin memory has previously been supported.

A second possibility is that memory durability may be determined primarily by post-encoding consolidation mechanisms that serve to integrate memories into new and existing cognitive schemas (Diekelmann & Born, 2010). A recent study using the same task and a similar paradigm to the current experiment provided evidence that episodic memories that go on to develop detailed durable representations *are not* characterized by additional BOLD activity during encoding beyond that required for successful retention after a short-delay (Sneve et al., 2015). This study applied a between-groups sample and tested 74 participants on an associative-source memory task either after a delay of ~1.5 hours or ~6 weeks. As such, the long-delay interval ensured that the events recalled with source memory had indeed established durable traces in participant episodic memory. While not strictly in direct support of the role of offline post-encoding processes in determining memory durability, the study did provide compelling evidence against the encoding-intensity hypothesis; the longest-lasting durable memories do not seem to simply be the product of the strongest activations in memory networks observed under encoding.

To reconcile this with previously discussed results showing an intensity-related encoding relationship, it may be that the use of confidence ratings (Liu et al., 2013) or forced-choice remember-know judgements (Uncapher & Rugg, 2005) may not have truly reflected episodic recollection. Indeed, it is possible that the reliance upon participant judgements of memory accuracy as opposed to an explicit test for contextual memory surrounding the event (such as the one used by Sneve et al., 2015) may result in a greater mixture of familiarity-based recognitions. In addition, all previous investigations employed quite small sample sizes (N=12; 18; 24). In the study by Carr and colleagues (2010), participants were instructed to intentionally commit encoding-stimuli to memory and tested on the same items after both delays, which makes comparisons with other durable memory investigations that all employed *incidental* encoding paradigms difficult. As such, it may be that the previously observed hippocampal activations under intentional encoding predicted durable memory for

words only when these had previously been reactivated during a test-retest procedure (Carr et al., 2010). Alternatively, memory over 48 hours or a one-week interval (the longest delay period tested where support exists for intensity-encoding) may follow an encoding-intensity principle, whereas alternative mechanisms may be at play in determining a memory's true longevity across weeks.

1.3. The Role of Post-encoding Consolidation

As one such alternative mechanism, durable memory development may depend to a greater extent upon offline processes occurring after encoding. It is well established that the subsequent development of a memory cannot be explained entirely by processes evident under encoding, because superior memory for episodic experiences is gained after a delay period involving sleep (Jenkins & Dallenbach, 1924). This concept of offline sleep-dependent consolidation has been confirmed in psychological literature spanning decades (see Diekelmann & Born, 2010; Stickgold, 2013). While difficult in itself to put to empirical test, research indicates that offline consolidation involves the reactivation of encoded memory traces through interactions between hippocampus and neocortical regions that governed the original perception (Born, Rasch, & Gais, 2006). Thus, the replay of learned memories is thought to involve the reactivation of previous neural patterns engendered at the time of encoding. Indeed, this re-engagement of encoding correlates is believed to be recurrent for processes of consolidation and retrieval (Carr, Jadhav, & Frank, 2011), and therefore follows a Hebbian account of learning across the memory lifecycle.

Evidence is now emerging for a theory of selective memory consolidation during offline post-encoding periods, whereby the evolutionary trajectory of a memory, in terms of whether it will become stabilised, integrated into existing cognitive schemas or discarded, may be determined during stages of sleep (see Stickgold & Walker, 2013). Research driving this theory is showing that memory tested after a nights sleep can be significantly enhanced post-encoding by the simple instruction to remember (Saletin, Goldstein, & Walker, 2011), the knowledge of a future memory test (van Dongen, Thielen, Takashima, Barth, & Fernández, 2012), the promise of monetary reward (Fischer & Born, 2009), and the subsequent gain of affectively salient information (Dunsmoor, Murty, Davachi, & Phelps, 2015). This indicates that one of the functions of sleep is to selectively promote remembering through offline systems consolidation, and that the expected future relevance of material is critical in determining the evolutionary pathway of a memory representation. Further, this holds even when saliency information is gained post-learning (see Dunsmoor et al., 2015). Moreover,

since post-encoding salient information was gained in a wakeful state, this implies an active wake-dependent process that highlights events-to-be-remembered (or forgotten) based on how relevant they are deemed for future behaviour (Wilhelm et al., 2011), which may dynamically interact with sleep-dependent mechanisms that further determine memory durability (Stickgold & Walker, 2013).

If a memory is to achieve a more durable representation, then, it must undergo further post-encoding consolidation by mechanisms that seem to operate on a selective basis. Under the first, intensity-encoding account, the experiences that initiated a higher level of neural processing under encoding would be the most likely candidates to become subject to post-encoding consolidation processes. Also in line with this, left hippocampal encoding activity has been shown to be indicative of the degree of consolidation achieved by post-encoding sleep (Rauchs et al., 2011). Conversely, under the second account, the selection of durable candidates may be determined perhaps solely by post-encoding mechanisms in the brain, provided that a critical threshold has been surpassed for memory representation in the short-term. Under this scenario, no differences in brain activity would be evident under the encoding of short-duration and long-duration recollections.

1.4. Complementary Durable Encoding Mechanisms

Although the aforementioned absence of additional BOLD activity between short and long-delay encoding conditions indicates that durable memory formation may be more a product of post-encoding consolidation processes, Sneve and colleagues (2015) did find evidence that a complementary pattern of increased right hippocampal connectivity with cortical perceptual areas and self-referential DMN areas may be causative in establishing the longest lasting memories. Given our knowledge about episodic memory re-activation, Hebbian logic would dictate that increased connectivity between hippocampus and neocortical perceptual sites at the time of encoding would serve to increase the synchronization of neuronal firing patterns between these modules. In turn, this strengthened connectivity may somehow interact with selective consolidation during sleep, possibly aiding with the offline transfer of information from hippocampus to the neocortex. In agreement with this, emotional memory research has found that amygdala connectivity with MTL structures under encoding was predictive of the durability of recollections (Ritchey, Dolcos, & Cabeza, 2008). More crucially for the present study, however, this finding was in the absence of univariate effects: no BOLD activation differences were found between the

encoding of emotional pictures that retained memory representation over a short-delay, and those that lasted one week.

Functional coupling of critical memory nodes may also persist into post-encoding resting states. Consistent with observations in animal research evidencing hippocampal replay of previously experienced behavior patterns in the awake state (Carr et al., 2011; Karlsson & Frank, 2009), imaging data in humans has shown that correlations in ongoing BOLD activity (putatively considered a measure of inter-regional connectivity) between hippocampus and perceptually-relevant regions persists into post encoding rest periods (Tambini & Davachi, 2013; Tambini, Ketz, & Davachi, 2010), and is related to individual differences in memory performance.

Thus, connectivity between key task-dependent neural structures may be a critical indicator of memory strength across time, suggesting that functional coupling of task-relevant brain regions during and post encoding is related to memory consolidation. In contrast, intensity-dependent neural activity, thought to reflect initial consolidation levels, may prove to be somewhat negligible in the formation of durable memories, at least once the network has exceeded the critical intensity-threshold needed for representation across a short delay. Thus, also under this somewhat complementary encoding scenario, no differences in the level of engagement of neural networks would be evident between short-duration and durable encoding.

1.5. Introduction to the Present Investigation

Taken together, ample support exists for an intensity-dependent encoding system in the short-term domain, whereas conflicting evidence exists for this in the long-term domain. The most compelling evidence, however, indicates that durable memory formation is *not* simply the product of greater activation levels at encoding (Sneve et al., 2015). Instead, a more likely candidate process for the formation of durable memories may be increased functional coupling between hippocampus and relevant structures observed 1) under encoding, 2) during post-encoding periods, and 3) during sleep. If these are the fundamental processes behind the transformation of short-duration weaker memories into more lasting durable representations, and the neuroimaging manifestation of this is reflected by increased connectivity between hippocampus and perception-related cortical modules, then no additional BOLD activity should be evident in brain activation signatures between short-duration and long-duration successful encoding. It is this claim that it tested here.

The specific aim of the present fMRI experiment was to corroborate evidence for this recent claim by replicating the results of a between-groups study (Sneve et al., 2015) using a within-groups sample with the potential to show higher sensitivity, due to the lack of between-subject variation. It is also plausible that the conflicting results of Sneve and colleagues could be attributable to it being the only fMRI durable memory study employing a between-groups sample. Thus, a within-subjects replication of key findings from this study would provide further evidence against the encoding-intensity hypothesis in the creation of durable memories, and would suggest that such conflicting results may be more attributable to the wavering reliability of previous paradigms to the extent that they tested true episodic memory. In comparing brain activity under encoding that leads to subsequent recollection after a short delay against encoding activity that leads to subsequent recollection after a duration of weeks, this tests both accounts of durable memory formation. Namely, evidence would be provided for the first, intensity-governed account by testing a) whether long-term memories follow a principle of encoding intensity, or b) whether this is only evident in the formation of short-term memories. A null finding to the former would imply that post-encoding processes, or complementary encoding mechanisms that do not reflect the degree neuronal recruitment, may be the primary mechanisms in determining the selection of durable memory candidates, and thus somewhat substantiate the second (or complementary) account.

Given the caveats of a re-constructive memory system (Schacter & Addis, 2007; Schacter et al., 2012), the oft-used remember-know paradigm is arguably a suboptimal operationalisation of memory, because it relies on participant judgments' of confidence as a classifier of true (remember) or partial (know) memory of a previously seen stimulus. As such, previous investigations probing durable memory may have included a greater mixture of familiarity-based memories under the classification of recollections, as opposed to testing a more exclusive sample of true episodic recollections that reflect the accurate retrieval of qualitative information surrounding the event. In support of this claim, a meta-analysis examining studies attempting to dissociate recollection and familiarity processes at the neural level found that participant-reported confidence levels were a poor predictor of these processes (Skinner & Fernandes, 2007). Thus, a further aim was to distinguish true-episodic memories from more familiarity-based ones. To achieve this, the present experiment used an fMRI paradigm in combination with a version of the subsequent memory paradigm (Brewer, 1998; Wagner, 1998) modified to include an associated action with each item at study. Subsequent recall of a previously seen 'old' item without the associated action was classified as an item-memory, whereas recall of both item and action was classified as a source memory

that reflected accurate recall of the contextual details of the event, and thus is believed to equate to recollection (Diana et al., 2007; Yonelinas, 2001). Participants were tested on different items after each delay. In the absence of explicit information regarding them, participants were believed to be naïve to the ensuing memory tests during initial encoding. An incidental procedure was applied under the rationale that this would allow post-encoding processes to occur in a manner more akin to everyday life. Here, both accounts of durable memory formation are put to the test, while allowing natural memory functions during sleep and post-encoding rest to play their part.

1.6. Hypotheses

Given the evidence summarised above, it was hypothesised that (1) contrasts of short-duration recollection memories versus both forgotten items and item-only memories would reveal an encoding-intensity explanation, characterized by $_{a)}$ increased activity in task-specific memory encoding cortical regions, and $_{b)}$ decreased activity in DMN regions. It was believed this explanation would also be evident at the subcortical level, namely through $_{c)}$ increased activity in hippocampus relative to both forgotten items and item-based memories. It was further hypothesised that an investigation into durable recollections would reveal that (2) this encoding-intensity principle would not be the mechanism underlying long-duration recollections, as evident by $_{a)}$ no-significant differences in hippocampus activation under the encoding of durable and short-lived recollections, and $_{b)}$ a non-significant finding at the cortical level for the same contrast.

2. Method

2.1. Subjects

A total of 26 healthy right-handed individuals (18 female) were recruited. All subjects were within the age range 18-35 (M=26.31, SD=3.45) and spoke Norwegian fluently. All reported normal or corrected-to-normal vision at the time of testing. Subjects were also unimpaired in hearing, and had no history of either neurological impairment or psychiatric disorders. Subjects had no history of serious injury or physical illness, chronic or otherwise. In addition, subjects reported no motoric difficulties, and none were taking any medication known to exert influence over central nervous system functioning. For inclusion, all were required to score > 28 on the Mini Mental State Exam (Folstein, Folstein, & McHugh, 1975), and < 20 on the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). As an incentive to complete all stages of the study, compensation of 1000NOK was

paid. Prior to their participation, all subjects received an information pack disclosing all necessary information. All participants were informed of their right to withdraw from the study at any stage without reason or prejudice, and were subsequently required to provide written informed consent. Ethical approval was granted by the Regional Ethical Committee of South Norway. Subjects who registered movement in excess of 2mm ($_{2/3}$ voxel size) in any of the six possible translations or rotations in the MRI scanner were excluded from all fMRI analyses. This affected the data for 4 participants.

2.2 Experimental Design

The experiment employed a within-groups rapid event–related fMRI design to investigate the brain mechanisms under encoding that lead to subsequent memory traces for episodic events becoming durable over time. The experiment aimed to replicate and extend recent between-groups findings from the Oslo-based Research Group for Lifespan Changes in Brain and Cognition (Sneve et al., 2015). All encoding and retrieval phases were performed inside the MRI scanner, although only functional encoding runs are focused on in the present paper. At encoding, participants were asked to decide whether a particular action could be performed on an item. The experiment therefore used a version of the subsequent memory paradigm modified to include an associated action with each encoded stimulus, based in-part upon a semantic decision for each (see Figures 1 & 2). This aimed to provide both a more robust measurement of true episodic source memory for the experimental stimuli, and a means of attempting to separate such memories from memories based more on a feeling of familiarity. Briefly, the encoding stimuli were 200 monochromatic line drawings of everyday objects and items, and participants undertook 4 encoding runs, each consisting of 50 item-action evaluations. Following the encoding of stimuli, participants received surprise memory tests at two separate timepoints: both ~1.5 hours post-encoding (T1), and an average of 21.0 days later (T2; 7-42 days later, SD=9.2). Each of the test phases consisted of 4 experimental runs composed of 50% 'old' items (i.e. items seen during the encoding phases), and 50% 'new' foils. All subjects were therefore exposed to a total of 400 images throughout the experiment. The overall experimental design was entirely participant driven; the independent variables were identified post-retrieval, and retrospectively applied to the experimental model to investigate brain activity exhibited during encoding. Thus, each item was categorized according to how it fared in participant memory in the hours (T1) or weeks (T2) following encoding. This categorization was achieved through a three-step procedure, where source memory of an item was operationalized by 1) its correct recognition, 2)

indicated memory for the previously associated action, and 3) correctly responding with the associated action (see Figure 2).

2.3. Encoding Runs

A central fixation cross lasting 10.5s was shown in the beginning, middle and end of each of the 4 encoding runs, providing an implicit baseline for BOLD activity estimation. The order of presentation of the 4 encoding runs was counterbalanced (50% ran in reverse order; 1-2-3-4; 4-3-2-1; see figure 1A) to control for potential order effects, such that half of participants received a memory test for items encoded under the first two encoding runs at T1, and half received a memory test for items encoded during the second two encoding runs at T1. An encoding trial started with an auditory presented question: a pre-recorded female voice asking either "can you lift it?", or "can you eat it?" in the Norwegian language. Questions were presented 25 times each during an encoding run in a pseudorandom order. One second after question onset, an image of an item was presented (subtending ~10 visual degrees in diameter). The order of appearance of visual stimuli was randomized. The experiment was designed such that during encoding the participant was likely to imagine lifting/eating the item in question in order to determine whether it was/was not possible, thus constituting an item-action association (Figure 1B). Items remained on screen for a duration of 2s, and appeared together with a response indicator bar that instructed participants which button to press to respond with a 'yes' [the item can be lifted/eaten] or 'no' [the item cannot be lifted/eaten]. This also provided visual feedback to the subject of their answer. The on-screen direction of button-response mapping was counterbalanced across participants to avoid confounds in the BOLD response relating to hemispheric biases associated with uneven motoric responses. Question and item were pseudorandomly paired, and attempts were made to counterbalance the feasibility of performing the action upon the item. Responses were logged using the NNL ResponseGrip system (NordicNeuroLab, Bergen, Norway). Participants had the 2s stimulus duration to record their response before the item was replaced by an inter-trial fixation cross. The timing durations of the inter-trial interval (ITI) were presented in a jittered fashion and lasted from 1-7 seconds (M=2.98, STD=2.49; exponential distribution over 4 discrete intervals). The jittering of event-related stimuli produced a high degree of timing variation under scanning that made possible the disentangling of overlapping haemodynamic responses due to the rapid presentation of stimuli. As such, the magnitude and shape of the BOLD response for stimuli falling into each of the encoding conditions could be more efficiently estimated (by producing less variable

estimates of parameters for each trial type), due to modeling of more weakly correlated regressors (Serences, 2004). It further reduced the likelihood of anticipatory BOLD responses prior to stimuli presentation due to expectation effects (Sirotin & Das, 2009), and allowed for the presentation of more stimuli within a given time period under the assumption that overlaps in the haemodynamic response are linear. The order of ITIs was also optimized using the optseq2 algorithm (http://surfer.nmr.mgh.harvard.edu/optseq/) to give the most efficient presentation schedule for the disentangling of overlapping haemodynamic events, and to achieve optimal time-usage in the scanner.

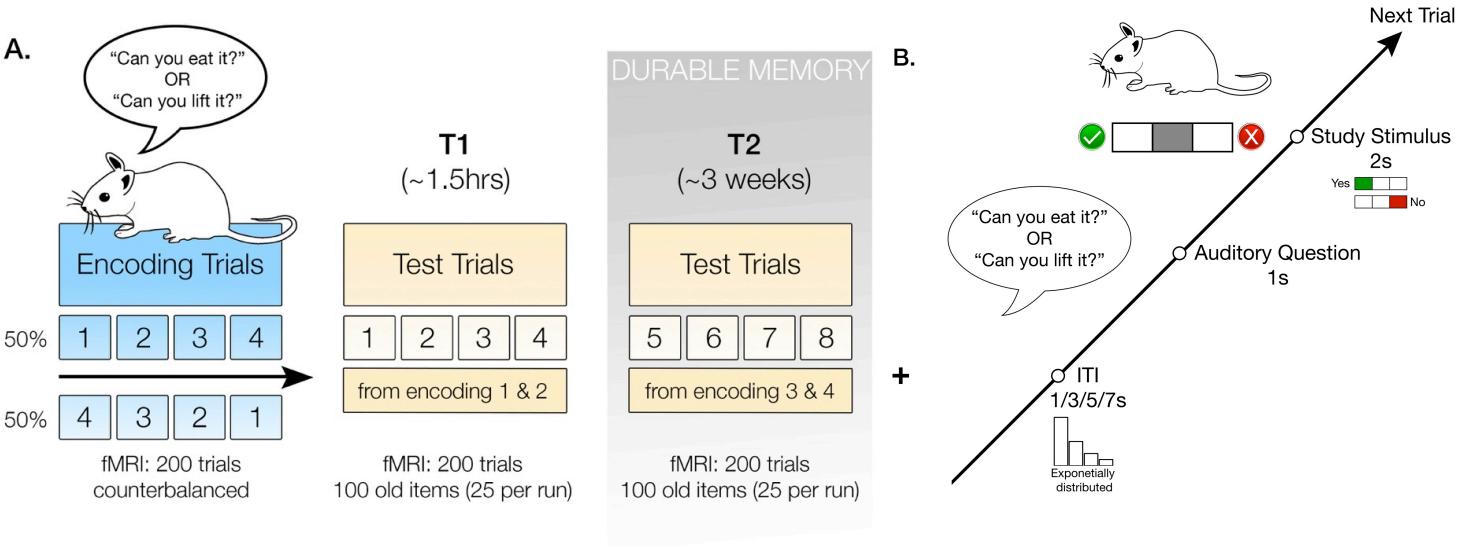

Figure 1. (A) Overview of experimental design. Participants encoded 200 item-action associations (over 4 encoding runs) and were tested upon these at two subsequent timepoints: T1 (~1.5 hours later) and T2 (~3 weeks later). The order of the 4 encoding trials was counterbalanced (50% ran in reverse order), such that half of participants were tested at T1 for items initially encoded and half were tested at T1 for items encoded under the latter two encoding runs. (B.) Timeline of an encoding trial. Intertrial intervals (ITIs) were presented in a jittered fashion. An auditory question was presented through participant headphones and 1 second later a visual stimulus appeared for a duration of 2 seconds. Participants were required to respond with a 'yes' or 'no' response, according to whether they believed the action (*either* eat *or* lift) could be performed on the object.

2.4. Memory Tests

The fMRI test runs shared the same parameters as the encoding runs in terms of the visual stimuli used, stimulus timing considerations (i.e. the jittering of stimuli onsets) and the inclusion of the implicit baseline at the start, middle and end of each test run for 10.5s. A test trial began with the pre-recorded female voice asking the Norwegian equivalent of the question: "have you seen this item before?" This constituted the first question (Q1) in a three-question procedure (Figure 2), and was followed by the appearance of visual stimuli (i.e. item and response indicator – *see 2.3*) 1s after question onset. Each of the 8 test runs consisted of 25 'old' and 25 'new' items in a randomised order. Participants were to respond either 'yes' [they saw the item during the encoding phase] or 'no' [they had not seen the item before]

within the 2s duration limit that the stimulus remained on screen. Button-response mapping was again counterbalanced across participants. A ‘no’ response (or a missed response) to Q1 was followed by the ITI and a new trial, and categorised as either a *miss* (if the stimulus was ‘old’), a correct rejection (if the stimulus was ‘new’), or a missed response. A ‘yes’ response if the stimulus was ‘new’ was categorised as a *false alarm*. Thus false alarm trials were identified by a subject believing that (s)he remembered a previously unseen stimulus and answering accordingly. In these instances the flexibility of the test paradigm allowed for completion of the entire three-question procedure. A ‘yes’ response to an ‘old’ item counted as a recognition hit, although follow-up questions served to classify the memory as either a *source* or *item* memory. A ‘yes’ response to Q1 led to a jittered-duration inter-stimulus interval (ISI), followed by the question “do you remember what you were supposed to do with the item?” (Q2). As before, a ‘no’ response to Q2 resulted in a new trial, and ‘old’ stimuli trials were subsequently categorised as *item memory* trials. A ‘yes’ response indicated that the participant remembered the associated action and, following a 2s ISI, prompted the final control question “were you supposed to lift it or eat it” (Q3). At this stage subjects were given a two-alternative forced choice between the responses ‘eat’ [I was asked whether the item was edible during the encoding phase] and ‘lift’ [I was asked whether the item was liftable during the encoding phase]. A correct response to Q3 was categorised as a *source memory* trial. This indicated that the subject could recall both item and its associated action as experienced during an encoding trial undertaken either ~1.5 hours or several weeks earlier. Incorrect responses to Q3 were classified as an *item memory*.

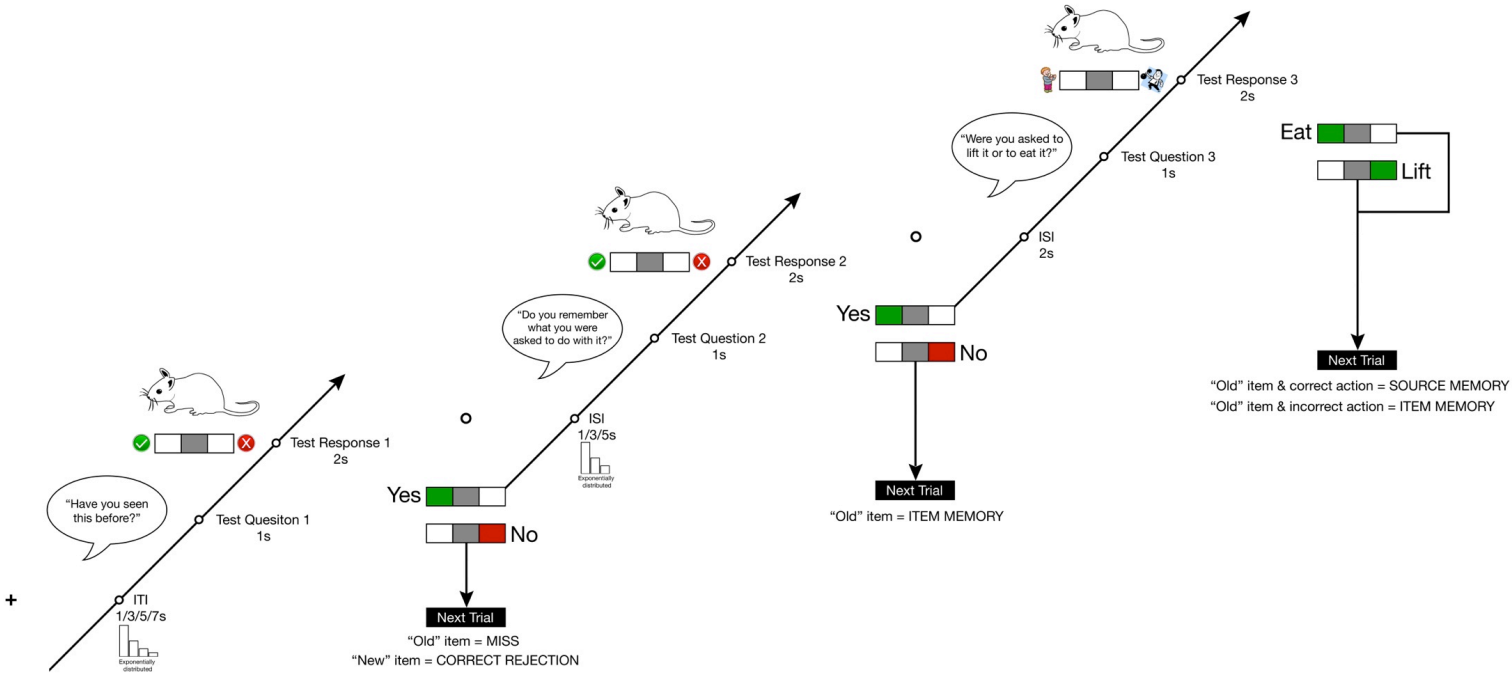

Figure 2. Timeline of a test trial. A trial consisted of up to 3 questions (Q1-3). Progression to the third question was dependent upon 'yes' responses to the two previous. Intertrial intervals (ITIs) and inter-stimulus intervals (ISIs) were presented in a jittered fashion for Q1 and Q2. Each auditory question was presented through participant headphones and followed 1 second later by a visual stimulus for a duration of 2 seconds. The stimulus was either 'old' (if presented during encoding phases) or 'new' (if not previously presented). Participants were required to respond with a 'yes' or 'no' response, according to whether they (1) remembered seeing the object, and (2) remembered the action they were asked to perform with the object. Q3 was a control question to classify whether the item was truly remembered with source memory through a forced choice two-alternative answer between encoding actions.

In sum, the participant-driven design made possible the categorising of encoding stimuli into conditions of *source memory* (correct response on all 3 questions), *item memory* (correct recognition but failure to recall the associated action) and *misses* (forgotten items), which could be retrospectively applied to a general linear model to identify BOLD activity that characterised the encoding of stimuli that subsequently fell into these memory conditions.

2.5. MRI Parameters and Equipment

Anatomical and functional data were acquired on a Siemens Skyra 3T MRI scanner. All encoding and test stimuli were presented on a NNL 32" LCD screen (resolution= 1920 x 1080 px; NordicNeuroLab, Bergen, Norway) viewed through a mirror mounted onto a Siemens 24-channel head-coil (Siemens Medical Systems, Erlangen, Germany). Auditory stimuli were presented via the scanner intercom to the participant's headphones. All stimuli were presented using the E-Prime 2.0 stimulus presentation software (Psychology Software Tools, Pittsburgh, PA), and stimulus presentation was synchronised with MRI image acquisition via a NNL SyncBox (NordicNeuroLab, Bergen, Norway). A T1-weighted magnetization prepared gradient echo (MP-RAGE) sequence was used for the anatomical scans of subjects composed of 176 sagittally-oriented slices acquired using a turbo-field echo pulse sequence with the following parameters: repetition time [TR]= 2300ms, echo time [TE]= 2.98ms, flip angle= 8, voxel size= 1 x 1 x 1mm, field of view [FOV]= 256x256mm. Prior to functional runs, static inhomogeneities in the magnetic field were characterised by a b0 field map (Jezzard & Balaban, 1995), which was subsequently used to distortion-correct BOLD T2*-weighted echo planar images (EPI). Functional data were acquired using a BOLD sensitive T2*-weighted EPI sequence, and imaging parameters were common to all task fMRI runs. Each EPI volume consisted of 43 transversally-oriented slices (covering the entire cerebral cortex and most of the cerebellum) with no gap in between slices: TR= 2390ms; TE= 30ms; flip angle= 90°; voxel size= 3 x 3 x 3mm, FOV= 224 x 224mm. All

scans were taken using a GRAPPA acceleration factor of 2, a parallel imaging technique used to reduce scan time and thereby limit the risk of motion artefacts as a result of participant discomfort (Lindholm et al., 2009). Slices were taken using interleaved acquisition. The first three functional runs were taken as dummy volumes to compensate for the effects of an imperfect flip angle (T1 saturation effects that occur when high-energy state protons are first subjected to a radiofrequency pulse), and to accustom the subject within the scanner environment. These volumes were subsequently discarded from the time-series under the analysis. 131 volumes were produced for each of the functional encoding runs. The number of volumes produced during functional test runs was dependent upon participant memory performance (~200 volumes): in general, participants who performed better received more questions, therefore amounting to increased functional volumes. However, only functional encoding runs are analysed in the current paper.

2.6. Preprocessing of Structural MRI Data

The T1-weighted anatomical images were subject to reconstruction of the cortical mantle and volumetric segmentation of the subcortical structures using the Freesurfer 5.3 image analysis suite (http://surfer.nmr.mgh.harvard.edu/). Briefly, this included methods to motion-correct the anatomical images and average across scans in the case of multiple volumetric T1 weighted inputs (one subject due to excessive motion) (Reuter, Rosas, & Fischl, 2010), isolation of the brain by removal of non-brain tissue from the T1 weighted image using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), computation of the Talairach transformation matrix (12 DOF), uniform normalisation of the scanner coil intensity bias (Sled et al., 1998), segmentation of the subcortical white matter and deep grey matter volumetric subcortical structures (such as hippocampus, amygdala, caudate, putamen, ventricles) (Fischl et al., 2002), white matter segmentation and subsequent tessellation of the grey matter/white matter boundary, automated topology correction, and surface deformation following intensity gradients to demarcate the white matter-grey matter and grey matter-pial surface boundary lines at the locations where the greatest intensity shifts delineated the transition between tissue classes (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000). Leading on from this cortical surface modeling, further processing steps included surface inflation, registration of individual cortical models to a spherical atlas based on folding patterns which served to align cortical geometry at the group level (Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999), and parcellation of the cortex into probabilistic units relative to sulci and gyri placement (Desikan et al., 2006). Such methods have

demonstrated robust test-retest reliability across both varying scanner manufacturers and magnetic field-strengths (Han et al., 2006) (see http://freesurfer.net/fswiki/FreeSurferMethodsCitation). Cortical reconstructions were subsequently quality-checked, and manual edits of white-matter or pial boundaries were (conservatively) made where necessary (2 subjects).

2.7. Preprocessing of fMRI Data

Preprocessing of the functional imaging data from the encoding runs was performed using the Freesurfer Functional Analysis Stream (FSFAST) version 5.1 (https://surfer.nmr.mgh.harvard.edu/fswiki/FsFast). All functional encoding runs were first distortion-corrected using b0 field maps taken to characterize the static field inhomogeneities evident in the T2* weighted scans as a function of magnetic susceptibility differences in neighbouring tissues (Jezzard & Balaban, 1995). These maps can be applied to reduce the impact of artefacts that would otherwise result in reduced signal and increased distortions, particularly in medial inferior frontal and temporal areas. This was performed using the FMRIB Software Library (FSL) PRELUDE (phase map) and FUGUE (smoothing of voxel shift maps and dewarping) functions (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FUGUE). Following this, functional images were corrected for participant motion using AFNI's 3dvolreg (http://afni.nimh.nih.gov). Motion-correction parameters were programmed to correct and register all images to the middle time-point in each run. Due to the non-simultaneous acquisition of functional slices, images were slice-timing-corrected to the middle TR in a volume to account for the interleaved acquisition of the composite slices of a volume. Functional images were uniformly normalised in their intensity to account for scanner intensity bias, and were subsequently co-registered to the T1-weighted anatomical scans of participants. Next, functional data that corresponded to the cerebral cortex was resampled onto the reconstructed left and right cortical surface for each subject, and 4D data that corresponded to subcortical structures was realigned into MNI305 volume space, estimated with 12 degrees of freedom using a linear transform. Lastly, a Gaussian kernel of FWHM 8mm was applied to smooth functional data on each surface at every volume taken (2D surface-based smoothing). Critically, such surface based-smoothing may be more optimal than volume-based smoothing because it respects the fact that brain function follows the complex topography of the cortex, and therefore does not smooth function across gyri. Rather, smoothing occurs across vertices (defined by a freesurfer co-ordinate system) that follow the folds of the cortex. Finally, a high-pass filter with a cutoff of 0.01Hz was applied

to the time-series data to remove low frequency drifts, and the temporal-autocorrelations in the residual noise of the BOLD time-series were dealt with using temporal prewhitening methods.

2.8. Planned Analyses: Source Memory Encoding

2.8.1. Configuring the general linear model. The onset-time and stimulus durations of each encoding event of interest were modelled by the canonical haemodynamic response function: a double-gamma convolution that includes the post-stimulus undershoot. These events of interest constituted regressors that allowed fitting of a general linear model (GLM) to the observed BOLD response during encoding trials.

The first-level GLM design matrix consisted of the following regressors: items for which participants were later found to retain a *source memory,* items for which participants were later found to retain an *item memory* and items for which participants were later found to have forgotten (*miss* trials) (see Figure 2). Additionally, the temporal derivatives for each of these 3 conditions were included as regressors to improve the model fit by accommodating for slight temporal variations in the haemodynamic response function across voxels. A fourth regressor of no interest was included in the design matrix that modelled stimuli for which participants did not respond to Q1 within the 2-second timeframe. This fourth regressor was only included to account for the elements of the BOLD time-series that could be explained by the presentation of stimuli, and was not subsequently used for any further analysis. A set of nuisance regressors, including motion-correction parameters obtained during the realignment stage and a set of polynomials (up to the order of 2) were also included in the GLM to model some of the known components of the time-series data that result in noise.

2.8.2. Short-delay contrasts: cortical level. Next, contrasts were computed for the beta coefficients on an individual basis for each of the 3 regressors of interest (*source memory, item memory, miss*) relative to the implicit baseline at T1, and entered into a random-effects model at the group level. In addition to these baseline contrasts, the following contrast images were calculated and brought to the group level for T1 memory performance: *memory vs miss, item memory vs miss* and *source memory vs item memory*. The output of all contrasts was converted to the percentage BOLD signal change between conditions. The FSFAST processing stream allowed for group-level tests of statistical significance between encoding condition contrasts to be computed for every vertex on the cortical mantle, independently for the left and right reconstructed hemispheres. All subjects were treated as random-effects to

account for both within and between-subject variance, and both ordinary least squares (OLS) and weighted least squares (WLS) GLM analyses were carried out for all contrasts of interest. Whereas OLS gives equal weight to all subjects when calculating the mean beta coefficients on a vertex-wise basis, WLS reduces the influence of subjects that would otherwise provide more 'noisy' data to the model. This effectively de-weights subjects with greater variance in BOLD response through inputting the variance maps computed by the first-level GLM into the model, and weighting subjects by the inverse of this first-level variance (Thirion et al., 2007). It was therefore predicted that WLS analyses should yield more precise parameter estimates by being less noise-driven. However, since this also likely down-weights the influence of poorly performing subjects (potentially making investigation of individual differences problematic), OLS analyses were performed as an additional quality check.

2.8.3. Short-delay contrasts: hippocampus. To evaluate the encoding-intensity account on the subcortical level after a short-delay, the left and right hippocampus were defined *a-priori* as regions of interest, and values were extracted for the percentage BOLD signal change between contrasts for each subsequent memory condition at T1 relative to the implicit baseline. Next, paired-sample *t*-tests were performed between these baseline contrasts in the left and right hippocampus for *source memory v miss,* and *source memory v item memory*, under the rationale that hippocampus should show preferential recruitment during the formation of short-delay tested source memories.

2.8.4. Long-delay contrasts: hippocampus. Similarly, paired *t*-tests were performed between hippocampal encoding activity leading to *T1 source memory v T2 source memory*, under the rationale that any delay-related differences in encoding activity would indicate that durable memories involve differential engagement of hippocampus relative to short-duration memories.

2.8.5. Long-delay contrasts: cortical level. The *source memory v baseline* contrast was computed for subsequent source memory after a long delay (T2) and tested for statistical significance on a vertex-wise basis. A within-subjects contrast (*short-delay v long delay*; *T1 v T2*) then tested whether brain activity observed under encoding can predict whether a source memory becomes durable over time. Importantly, only the *source memory v baseline* contrast was deemed relevant for T2 analysis, since one can infer that all items recalled with source memory at T2 would also have been recalled with source memory at T1 (Liu et al., 2013;

Uncapher & Rugg, 2005), whereas item memories at T2 may have resulted in source memories if tested after a short delay.

2.8.6. Cluster-wise correction for multiple comparisons. All resulting significance maps were corrected for multiple comparisons using a cluster-based correction approach, defining a cluster as a set of spatially contiguous vertices above a given threshold. Specifically, this correction method performed Monte Carlo simulations that determined the maximum cluster size likely to be obtained under the null hypothesis across 10,000 iterations with a vertex-wise threshold of $p < .05$, and corrected for the number of times where this number exceeded the maximum cluster size of the observed data, thus returning a cluster-forming threshold of $p < .05$. This resulted in clusters that had been corrected for multiple comparisons across the cortical surface (Hagler, Saygin, & Sereno, 2006; Hayasaka & Nichols, 2003).

3. Results

3.1 Behavioural Results

25 participants were shown a total of 200 item-action associations during encoding and tested for subsequent memory of these at two different time-points (100 items at T1; 100 items at T2). After a short delay of ~1.5 hours (T1), participants were able to recall on average 48.64% (SD=14.64%) with source memory, 15.6% (7.31%) with item memory, and had forgotten 28.12% (13.22%) of items shown during encoding (Figure 3; test trials that could not be characterized by item/source memories + missed trials account for the remaining %). When participants were tested after a delay of ~3 weeks (T2) on the remaining items seen at study, source memory performance was significantly lower ($p < 10^{-13}$), measuring 7.8% (4.93%). There was a trend towards significantly greater item-memory observations at T2 than T1 ($p = .09$), indicating a tendency towards more familiarity-based memories after a long-delay. After a long-delay, participants were found to remember on average 18.56% (11.11%) with item memory only, and had forgotten 68.48% (17.78%) of items shown under encoding. Unsurprisingly, many more items were forgotten from T1 to T2 ($p < 10^{-11}$).

To test whether the method of counterbalancing of encoding runs was sufficient to account for potential order-effects of presentation across participants, independent sample *t*-tests were performed between the two counterbalancing groups (encoding run presentations 1-2-3-4 / 4-3-2-1; see Figure 1A) and Bonferroni-corrected for multiple comparisons. These revealed no significant difference between encoding run presentation order and source

memory retrieval at T1 ($t(23) = -5.85$, corrected $p = .56$), nor at T2 ($t(23) = 1.87$, corrected $p = .14$). This indicates that behavioural data cannot be explained by order-effects, and that the counterbalancing method was adequate.

In addition to analysing source memory performance, recognition memory performance was also investigated. To account for potential differences in guessing behaviour, *d*-prime scores were calculated. *D*-prime (d´) gives a measure of a subject's true ability to distinguish 'old' from 'new' stimuli in memory, accounting for both recognition hits and false alarms. A paired *t*-test revealed recognition memory was significantly higher at T1 (d´ $M = 2.25$, $SD = .41$) than at T2 (.56, .32), $t(24) = 18.36$, $p < 10^{-15}$. However, one-sample *t*-tests for T1 ($p < 10^{-19}$) and T2 ($p < 10^{-9}$) *d*-prime scores tested significant against zero, indicating that recognition memory was significantly above chance level after each delay, and implying that subjects did not tend towards guessing behaviour. In addition, a paired *t*-test revealed that subject criterion C (an indicator of one's threshold level to produce a 'yes' response) was significantly lower at T1 (.58, .29) than at T2 (.90, .45), $t(24) = -3.35$, $p = .003$, indicating that subjects answered more conservatively with 'yes' responses after a long-delay. Thus, the latter two analyses give greater confidence that the observed source and item memories were a result of true recollection and familiarity memories, respectively.

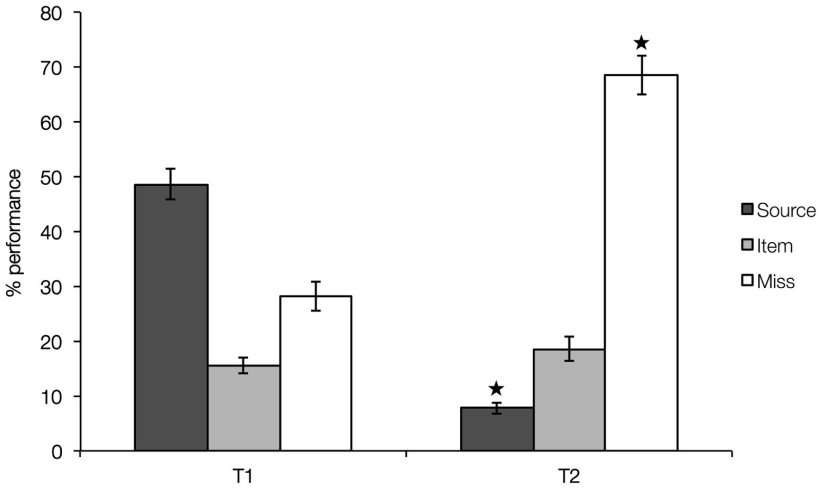

Figure 3.1 Behavioural results from the short (T1; ~1.5hrs) and long (T2; ~3 weeks) source memory tests. The number of source memory hits reduced significantly with time, whereas there was a trend towards greater item memories from T1 to T2 ($p = .09$). Naturally, significantly more items were forgotten at T2. * $p < .001$ percent change from T1. Error bars denote standard error of the mean.

Note that the proceeding results section is divided into two: the first part (3.2) investigates the aforementioned planned fMRI analysis comparisons, whereas the second part (3.3) conducts further exploratory fMRI analyses inspired by some unexpected and intriguing findings from the behavioural results observed.

3.2. fMRI Univariate Analyses: Source Memory, N=16

The large average drop in source memory between T1 and T2 indicated that some participants only showed source recollection for a few encoding stimuli after ~3 weeks. A minimum threshold for inclusion in the proceeding analysis was consequently set at 5 trials remembered with source at T2 (5%). This was deemed necessary, as inputting too few data points leads to more unrepresentative mean estimates (due to greater risk of sampling error). In turn, this returns noisier regression estimates. Consequently, 6 participant datasets had to be excluded for the proceeding analysis.

3.2.1. Short-delay contrasts: cortical level. The results of each T1 *memory condition v implicit baseline* contrast fitted using a WLS approach are shown on the cortical surface in figure 4. As such, figure 4 shows the BOLD encoding activity associated with both stimulus presentation and the respective subsequent memory condition that encoding stimuli fell into at T1. Clearly similar patterns of BOLD activation were observed for all encoding conditions relative to the implicit baseline in a distributed cortical network (threshold $p < .05$, corrected), and significant deactivations in DMN regions were observed, including vmPFC and ACC.

Although significant deactivations remained after correction only for item memory

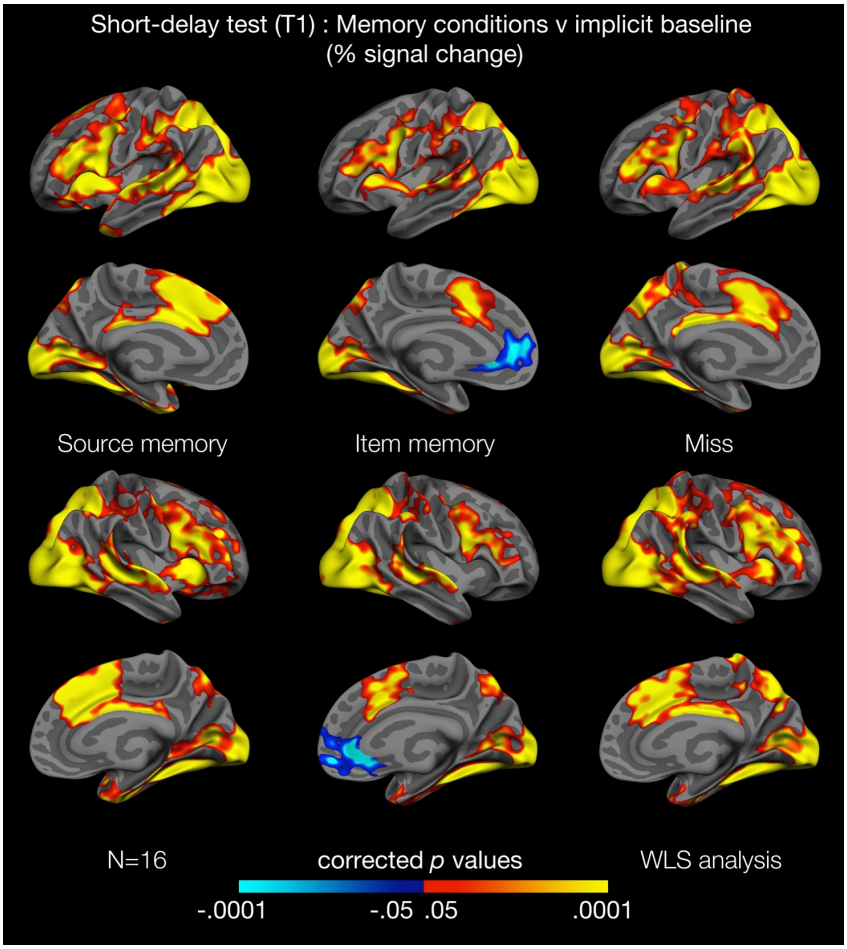

Figure 4. Results of *memory condition v implicit baseline* contrasts. A bilateral distributed network of activated cotical regions was found to lead to subsequent source memory (recollection), item memory (familiarity) and misses (forgotten items). Default-network structures with significantly reduced activation were also evident (see also Appendix A for uncorrected data). Top row: left lateral view; second row: left medial view; third row: right lateral view; bottom row: right medial view. All clusters corrected for multiple comparisons and thresholded at $p<.05$.

encoding, uncorrected data indicates the presence of characteristic DMN deactivations in all memory conditions, suggesting that these perhaps lay below the threshold for significance (see Appendix A). (Note that, although all proceeding visuals and interpretations are based on contrasts that have been corrected for multiple comparisons, the author found it prudent to include uncorrected supplementary data in appendices to aid with the interpretation of results).

Next, pair-wise contrasts between memory conditions at T1 were performed. All three pair-wise contrasts resulted in significant clusters of activation, lending support for the encoding-intensity hypothesis for episodic memories that last a short delay.

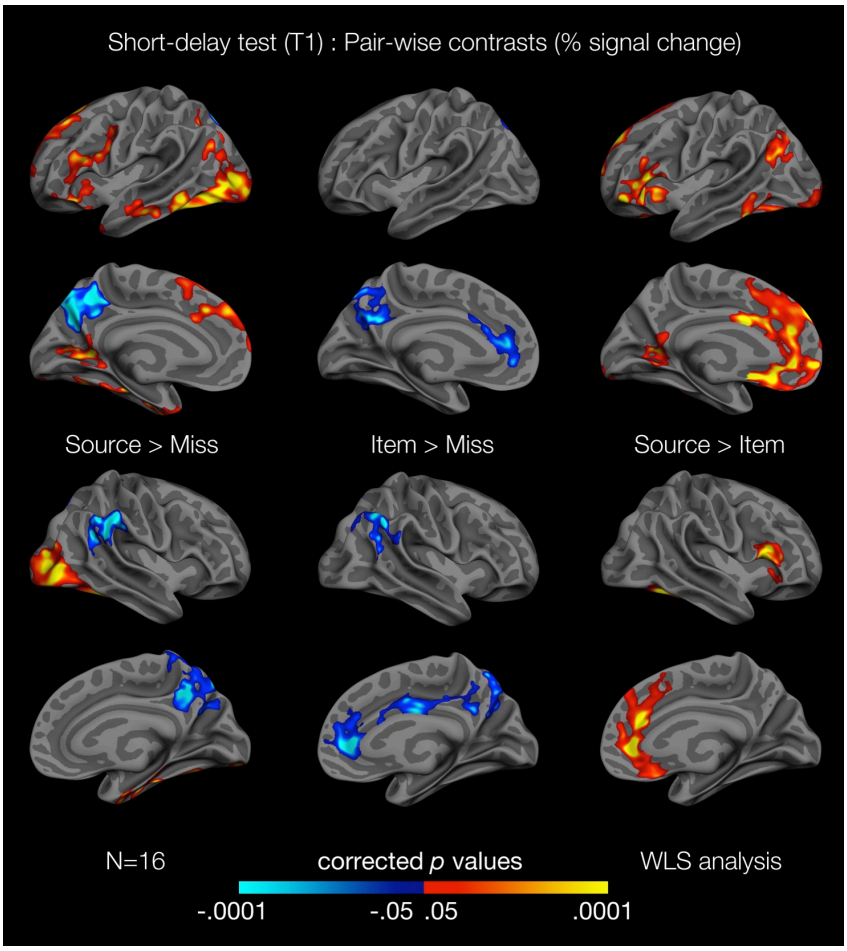

Figure 5. Results of pair-wise contrasts for memory conditions. Significant activations and deactivations were found in episodic encoding networks for both source memory relative to forgotten items (*source v miss)* and source memory relative to item only memories (*source v item*). Top row: left lateral view; second row: left medial view; third row: right lateral view; bottom row: right medial view. All clusters corrected for multiple comparisons and thresholded at $p<.05$.

Greater BOLD activation was observed in several anterior and posterior cortical areas, both for the encoding of source memories relative to the encoding of stimuli that were subsequently forgotten, and for the encoding of source memories relative to item memories (Figure 5). Greater activated brain regions were identified under source memory encoding in fusiform gyrus, lateral occipital cortex, superior frontal cortex, middle temporal cortex and precentral gyrus (M1). Furthermore, DMN cortical areas were identified as significantly less active for source memories relative to misses in bilateral precuneus and right supramarginal

gyrus. Comparable regions of decreased activation with the addition of anterior cingulate cortex were identified for item memories relative to miss responses. Together, this indicates that such additional cortical activations and deactivations are facilitative to the encoding of episodic memories and their retainment over a short delay. Further, a comparison of *source memory v item memory* encoding revealed significant activated clusters in bilateral superior frontal cortex, medial orbitofrontal cortex and anterior cingulate, implying that the additional engagement of these regions resulted in the development of source memories relative to item memories that lasted a short-delay (T1).

As a form of quality control for T1 results, comparable implicit baseline and pair-wise contrasts were performed on the entire sample not excluded due to motion at T1 (N=22). In general, there was very high agreement between sample sizes (see Appendix B). Additionally, to investigate the influence of analysis type upon the BOLD activation results observed thusfar, comparable baseline and pair-wise contrasts were submitted to a GLM analysis using OLS methods. While there was extremely high agreement between analysis types (see Appendix C), output from the WLS analysis appeared to yield more robust pair-wise activations. Because smaller sample sizes and fewer observations will yield greater variance around the true mean, a WLS approach was deemed likely to prove more robust for the present experiment. Therefore, this approach was used to visualise all further analyses.

3.2.2. Short-delay contrasts: hippocampus. Firstly, paired sample *t*-tests revealed a significant difference between encoding activity leading to miss trials (M= .03, SD= .07) and encoding activity leading to source memory (M= .08, SD= .05) at T1 in the left hippocampus, $t(15) = -2.90$, $p = .01$, and a marginally significant difference for the same comparison in the right hippocampus (miss M= .04, SD= .05; source M= .07, SD= 07; $t(15) = -2.13$, $p = .05$) (Figure 6; note no correction methods were applied due to the planned nature of these comparisons). Secondly, a significant difference was found between source and item memory encoding in left ($t(15) = -2.83$, $p = .01$) and right ($t(15) = -2.56$, $p = .02$) hippocampus at T1, revealing that hippocampus elicited greater activation during source memory encoding than during item memory encoding.

Thus, it is evident that BOLD activity in both a distributed cortical network (Figure 5), and in the hippocampus (Figure 6), follows a principle of encoding intensity for short-lasting memory representations, whereby the greatest activations were elicited to stimuli that became

strongly encoded in memory to the point where both item and the associated action were recollected at T1.

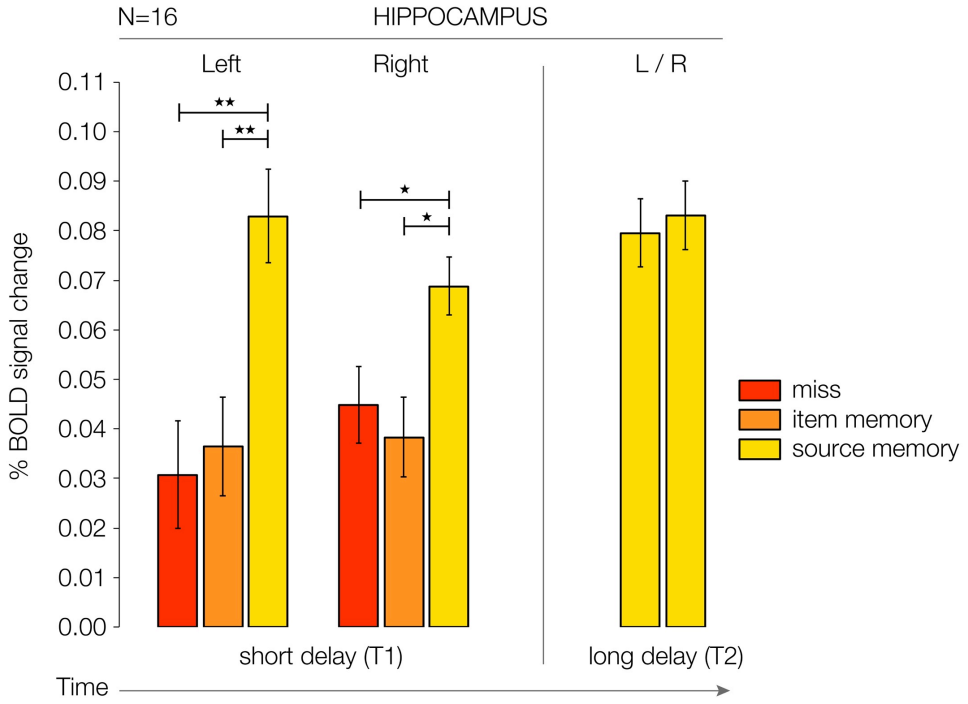

Figure 6: BOLD values extracted from the left and right hippocampus under the encoding of stimuli that subsequently fell into each memory condition (*miss*; *item*; *source memory*) *v baseline* after a short and long delay (T1, T2, respectively*).* ***p*= *.01*.**p* <= .05. Error bars denote 95% confidence intervals using the Cousineau method developed for within-subject designs (Cousineau, 2005).

3.2.3. Long-delay contrasts: hippocampus. Having found that the encoding of T1 source memories was subserved by greater hippocampal engagement relative to T1 miss and item trials, it follows that a significant difference between *T1 and T2 source memory* encoding would indicate that the encoding of durable source memories requires differential engagement of the hippocampus. No significant differences were found between T1 and T2 source memory BOLD activity for either the left (*p*=.89) or right (p=.49) hippocampus, implying that the encoding of durable source memories does not seem to be underpinned by greater hippocampal engagement relative to source memories that survive a short delay (see Figure 6).

3.2.4. Long-delay contrasts: cortical level. To investigate whether the encoding-intensity account is true of durable memories at the cortical level, a final contrast was set up for *source memory v baseline* conditions across the long and short time intervals (*T2 source v T1 source*). Figure 7 shows the (main planned) results. Two activated clusters in the right

inferior and superior parietal lobe survived correction, suggesting that additional activity here could be linked to durable memory formation (see also Appendix E).

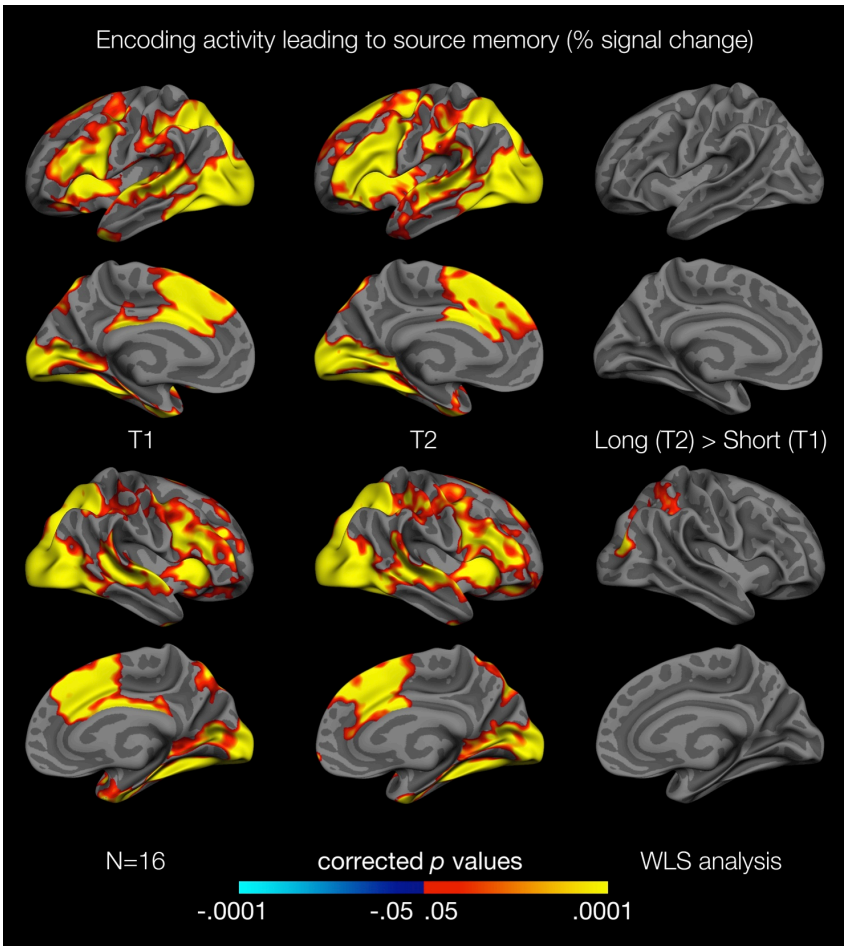

Figure 7. Results of *source memory v baseline* contrasts for source recollections that lasted a short delay (T1) and a long delay (T2). A similar bilaterally distributed episodic-network was observed for the encoding of T1 and T2 source memories. The third column shows the results of a *T2 source memory > T1 source memory* contrast. Two clusters in the inferior and superior parietal lobe survived. Top row: left lateral view; second row: left medial view; third row: right lateral view; bottom row: right medial view. All clusters corrected for multiple comparisons and thresholded at $p<.05$.

3.3. Exploratory Analysis

3.3.1 Cross-study comparison of behavioural results. To further explore the large drop in source memory between T1 and T2, cross-study comparisons were performed against previous research using the same paradigm on a between-groups sample (Sneve et al., 2015), and Bonferonni corrected for 4 comparisons ($\alpha = .0125$). Independent-sample *t*-tests revealed a significant difference between the two studies in durable source memory (current M = 7.8%, SD = 4.93%; previous M = 20.4%, SD = 10.1%; $t(55.81) = -6.63$, $p < 10^{-7}$, equal variances not assumed), and durable item memory (current M = 18.56%, SD = 11.11%; previous M = 30.0%, SD = 11.0%; $t(60) = -3.98$, $p < .001$). No significant differences were found for either source ($p = .08$) or item memory performance ($p = .17$) after a short delay of ~1.5 hours. Thus, despite an extra ~3 weeks difference between encoding and long-delay test in the study by Sneve and colleagues, T2 subject memory performance was much worse in the present study.

3.3.2. Median-split analysis: behavioural results. Perhaps subjects who demonstrate higher T1 source memory performance show an equally enhanced ability for recalling durable T2 source memories? This could possibly hint at a relationship between one's ability to encode short-lived and durable memories. To explore how T2 source memory performance relates to performance at T1, participants were grouped into high or low T1 performers according to whether their score fell above or below the sample median (50%). A repeated-measures ANOVA was performed on source memory with time (T1/T2) as a within-subjects factor and T1 source memory (high/low) as a between-subjects factor. A significant interaction was found between Time and T1 source memory, $F(1,23)= 55.05$, $p < .001$, in addition to a main effect of time, $F(1,23)= 634.18$, $p < .001$.

In probing this interaction, T2 source memory performance for the two groups was submitted to an independent samples *t*-test, under the rationale that a significant difference at T2 would indicate that the two groups simply differed in their encoding ability consistently over time. A non-significant difference was found at T2 between T1 high performers (M = 8.0%, SD = 5.7%) and T1 low performers (7.5%, 4.2%), $p = .81$, indicating that higher short-delay source memory encoding ability did not translate to improved durable source memory performance (Figure 8). Quite contrary, it demonstrates that T1 high performers had a greater percentage drop-off in source memory than low performers in the weeks between memory tests.

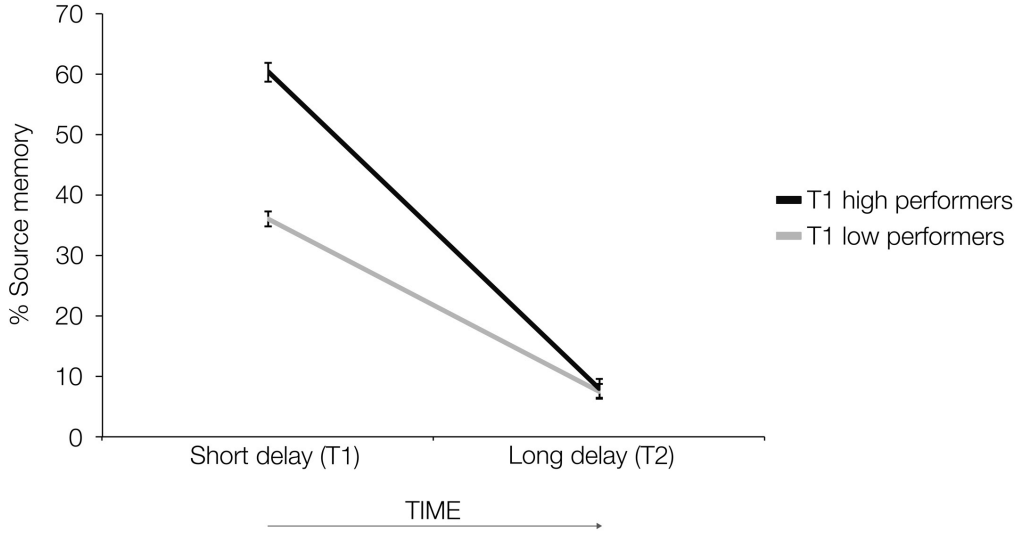

Figure 8: Subjects were classified into groups of high or low performers at a short-delay memory test (T1) according to whether their source memory score fell above or below the sample median (50%). Higher source memory performance at T1 did not amount to higher source memory performance at T2. Error bars denote the standard error of the mean.

3.3.3. fMRI univariate analysis: recognition memory, N=21. Owing to the fact that a dramatic drop in source memory was observed between T1 and T2 that was specific to the within-groups design of the present study, the next part of the analysis was concerned with investigating encoding leading to *recognition memory* (i.e. memory irrespective of item or source categorisation). As discussed in the introduction, previous durable memory investigations may have been closer operationalisations of familiarity memory. Thus, the present study aimed to explore this possibility by concatenating memory types, in turn producing a novel analysis. This allowed for the inclusion of 5 additional subjects (N=21, one excluded due to subpar T2 memory performance), and a concurrent boost in statistical power related to the number of overall memory observations, particularly at T2.

A new GLM was set up modeling the following regressors: *recognition memory* (operationalised by correct recognition of 'old' items) and *recognition misses*. A third regressor of no interest was modelled for trials where no response was given to Q1. The FSFAST processing followed the same procedures as outlined in section 2.8.1. Firstly, each T1 regressor was contrasted against the implicit baseline, and secondly pair-wise against one another. All contrasts were entered into a random-effects model at the higher level.

The pair-wise *recognition memory v miss* contrast produced a map of the BOLD activity elicited during the encoding of *recognition memories* that last a short delay (Figure 9).

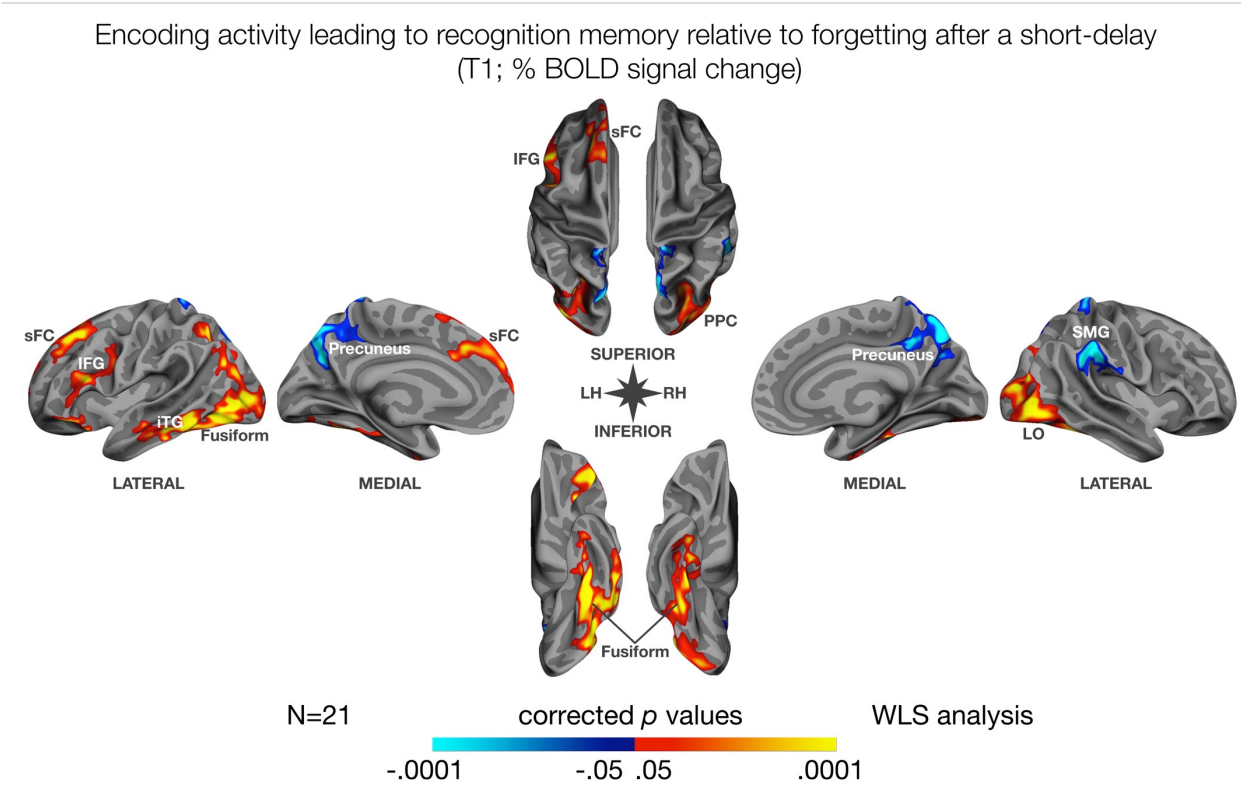

Figure 9: Encoding activity leading to *recognition memory* relative to *miss* (forgotten) trials after a short delay (T1). IFG: inferior frontal gyrus; sFC: superior frontal cortex; PPC: posterior parietal cortex; iTG: inferior temporal gyrus; LO: lateral occipital area; SMG: supramarginal gyrus. All clusters corrected for multiple comparisons and thresholded at $p<.05$.

Additional activity was observed in typical areas associated with episodic encoding, including bilateral fusiform, superior parietal cortex, inferior temporal gyrus and a lateral occipital area known to be involved in object-related processing (Grill-Spector, Kourtzi, & Kanwisher, 2001; Malach et al., 1995) and object-encoding (Cansino et al., 2002). Thus, the additional recruitment of both early-level perceptual regions involved in object recognition, and higher–level association areas seems to be facilitative to the encoding of memories that last a short-delay, irrespective of memory quality exhibited at test. Greater activation was also observed in right superior frontal cortex and inferior frontal gyrus, and significant deactivations were observed in typical DMN associated regions, including bilateral precuneus and right supramarginal gyrus, bolstering the notion that such deactivations are beneficial during memory formation (Daselaar et al., 2004) (see figure 9). Crucially, results were found to have very strong resemblance with earlier presented results (see Figure 5; *Source* > *Miss*).

Next, *recognition memory* was contrasted against the *implicit baseline*. Briefly, since this analysis is more sensitive to subject responder characteristics (or one's threshold for an internal 'yes' recognition response), the number of false alarms per subject was entered as a covariate to control for the number of recognitions that could be explained by chance (or as a consequence of implementing a low threshold (Stanislaw & Todorov, 1999)). As such, figure 10 displays the significance maps for *recognition memory* at T1 and T2, with the effects of false alarm rate partialled out of the model. Similar active and deactive encoding networks were observed for encoding activity leading to recognition memory at both timepoints (see also Appendix F for uncorrected maps).

Finally, to test the hypothesis of whether the formation of durable *recognition memory* is in part governed by processes under encoding, a *T2 recognition >T1 recognition* contrast was computed. Crucially, no significant clusters were found (cluster-wise, $p < .05$; Figure 10; see also Appendix F). Most interestingly then, the present results did not find support for the encoding-intensity account of durable memory formation for *recognition memory*, and thus argue against activation-intensity (reflecting immediate consolidation) as an encoding mechanism by which durable recognition memories are founded.

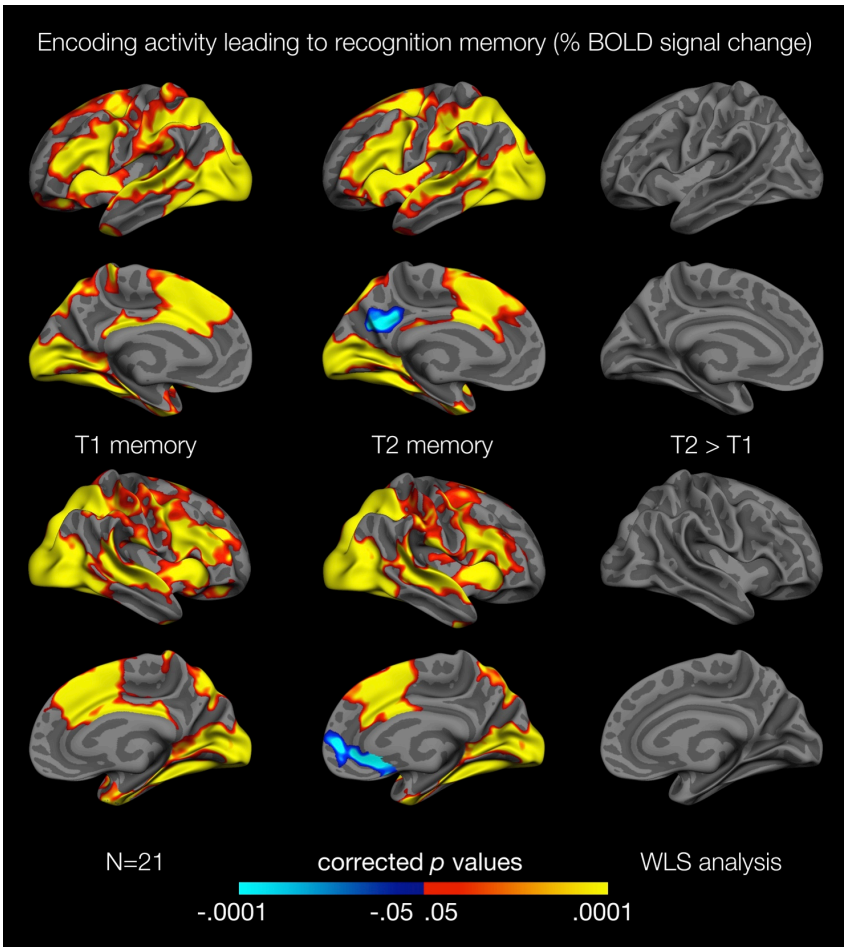

Figure 10. Results of *recognition memory v baseline* contrasts for encoding of short-duration (T1) and durable (T2) recognition memories. The third column shows the results of a *T2 recognition memory > T1 recognition memory* contrast. No significant clusters survived this time-wise contrast. All clusters corrected for multiple comparisons and thresholded at $p<.05$.

To test whether certain brain regions are associated more strongly with higher encoding ability, two separate GLM analyses were set up testing the correlational effects of T1 and T2 *d*-prime scores upon BOLD encoding activity. There was a significant main effect of activation in bilateral middle frontal gyrus, right superior frontal cortex and a posterior midline region upon one's ability to successfully encode T1 recognition memories ($p < .05$ corrected; Figure 11), and a significant main effect of activation in left inferior parietal cortex and bilateral superior frontal cortex upon one's ability to encode T2 recognition memories ($p < .05$ corrected). These main effects suggest that BOLD activity in these regions may be linked to the encoding of short-lasting and durable memories, respectively. However, a new GLM then modelled the interaction effect between T1 and T2 BOLD encoding activity and *d*-prime. Importantly, no significant interaction effect was found (figure 11, bottom), indicating no cortical regions were evident where BOLD activity related differently to recognition memory performance according to the encoding of T1 or T2 recognition memories (supplementary uncorrected significance maps also indicate that there were no apparent trends towards significance; see Appendix G).

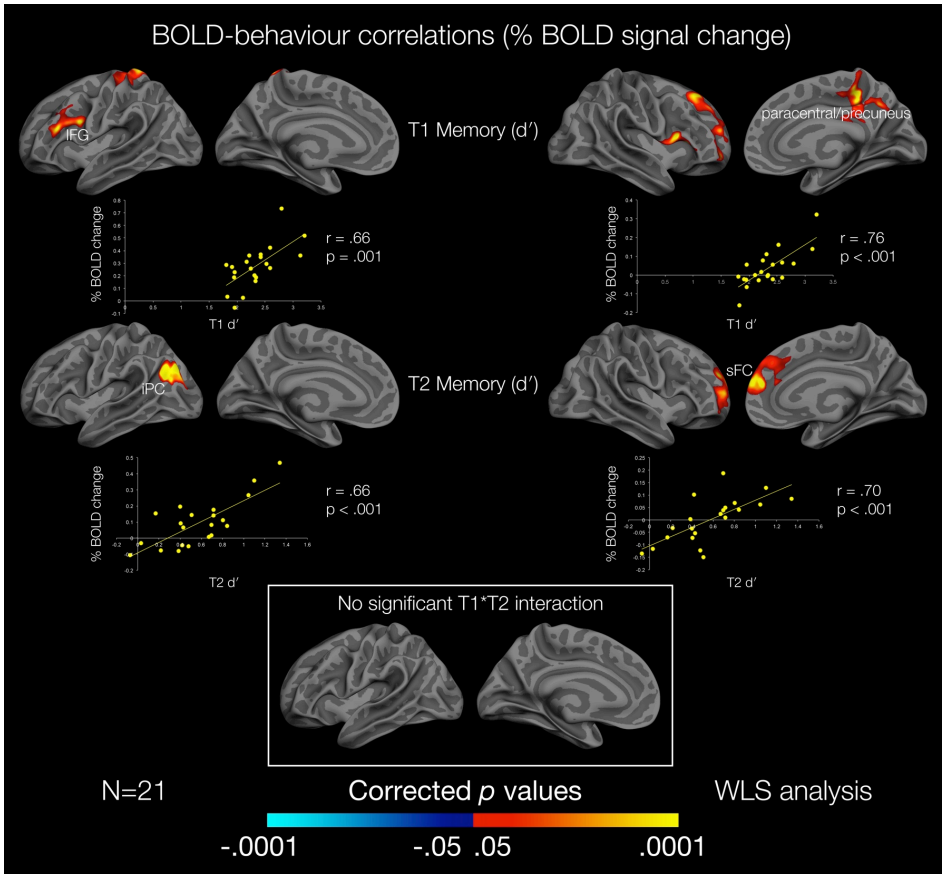

Figure 11. Brain regions that correlated with recognition memory (*d*-prime) at T1 and T2, and their interaction. No significant interaction effect was found of T1 and T2 *d*-prime scores upon BOLD activity. IFG: inferior frontal gyrus; iPC: inferior parietal cortex; sFC: superior frontal cortex. All clusters corrected for multiple comparisons and thresholded at $p<.05$.

3.3.4. fMRI univariate analysis: memory breakdown, N=21. Lastly, to further investigate the relationship between encoding activity and the apparent breakdown in memory processing systems evident between T1 and T2, a final GLM was set up. Here, all events associated with the presentation of stimuli were modelled as a single regressor against the implicit baseline and brought to the group level, yielding *encode-v-base* BOLD activity maps. Hence, BOLD encoding data was no longer dealt with as being associated with a memory test. In advance, data for all subjects was re-arranged into a temporal order, such that E1 (encode1) corresponded to the first two encoding runs undertaken, and E2 corresponded to the second two encoding runs undertaken (of encoding runs 1-4; see Figure 1A). Comparable procedures of processing were applied as outlined in section 2.8.1. A time-wise contrast of *E1 < E2* encoding activity was computed, under the rationale that a significant difference would indicate that differential encoding mechanisms are evident in the brain across time. The results suggest that bilaterally distributed encoding networks across the

brain were significantly less engaged during the encoding of later-viewed stimuli, than during the encoding of initially-viewed stimuli.

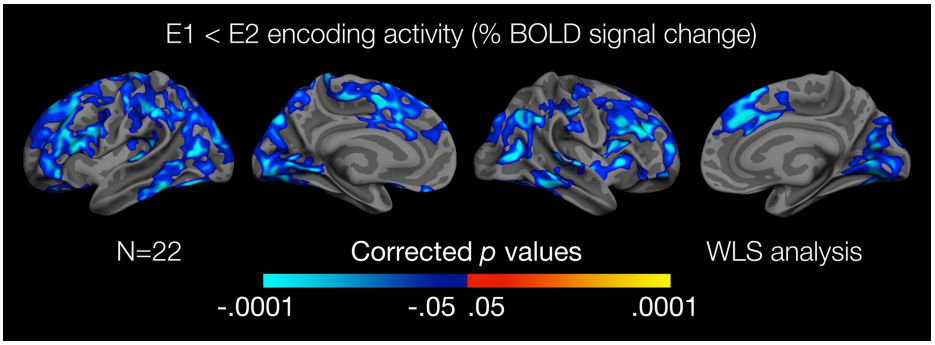

Figure 12: Data was rearranged into a temporal order (for encoding runs 1-4). A time-wise contrast of *E1 < E2* revealed the change in BOLD encoding signature between the first two encoding runs undertaken (E1) and the latter two encoding runs undertaken (E2). Widespread reduction in BOLD activation was observed in later encoding runs in regions corresponding to episodic networks. All clusters corrected for multiple comparisons and thresholded at $p<.05$.

4. Discussion

The aim of the current experiment was to substantiate recent research showing that the encoding of durable episodic memories is not associated with greater activation in episodic neural networks relative to activations observed leading to short-duration recollection, as measured by fMRI (Sneve et al., 2015). In the current study, a three-step procedure aided with the disentangling of episodic recollection (source) memories from more familiarity-based (item-only) memories. The present results provide evidence that the neural mechanisms engendered under the encoding of events that go on to develop as short-duration episodic memories fundamentally differ in an activity-dependent manner, such that the greatest activations in both hippocampus and cortical episodic-encoding networks predict memories that last over a short-delay, and their subsequent strength (i.e. as familiarity or source). In comparing encoding of short-duration and durable episodic memories, we found no evidence for additional hippocampal encoding activity, although cortical results suggest that the encoding of the most durable memory representations may be linked to additional activity in the right PPC. Further analyses that examined memory regardless of its subsequent strength (i.e. recognition memory) contributed a novel result: the development of durable recognition memory does not seem to be a consequence of an encoding system that demonstrates intensity-dependent activations beyond those that were required for successful representation across a short-delay. By extension, this result suggests that the selectivity of post-encoding offline consolidation processes does not seem to be governed by greater neural

recruitment in memory networks under encoding. Intriguingly, this is in contrast to what has previously been supported in the literature, although converges with and extends new evidence using the same paradigm (Sneve et al., 2015).

It seems, then, that surpassing a critical intensity threshold may be a prerequisite for encoded events to become represented in memory across a short-delay. Beyond this, alternate brain mechanisms may determine the selection from this initial 'pool' of candidate memories that will be become more robustly represented across time. A likely candidate process for this selectivity is offline post-encoding consolidation mechanisms in the brain that serve to re-engage memory representations via their encoded neural correlates during both waking rest and sleep. Although it is an intriguing possibility that complementary processes (e.g. levels of connectivity) under encoding help determine this selectivity, the present result provides evidence that durable memory formation does not seem to be related to higher activation levels that increase the likelihood for a memory's selection and further consolidation.

4.1. Hippocampus Findings

In the current study, intensity-dependent mechanisms that determine memory representation across a short delay were observed in subcortical structures. Specifically, the hippocampus was found to exhibit greater BOLD activity during the encoding of short-duration recollection memories relative to forgotten items. Of equal importance, differences in activation intensity were found between the encoding of short-delay-tested recollections and those only recalled with item-memory, that is, preserved recognition memory for encoding stimuli in the absence of recollection for the surrounding contextual details. This is in good agreement with previous research (Davachi et al., 2003), and data from patients with selective hippocampal lesions (Skinner & Fernandes, 2007), demonstrating dissociable neurocognitive mechanisms underlying recognition-based familiarity memories and memories that reflect truly recollective experiences at recall (Diana et al., 2007; Duarte, Ranganath, Winward, Hayward, & Knight, 2004; Yonelinas, 2001). The anatomical location of hippocampus has been proposed as optimal in the MTL amongst its surrounding structures that receive information from visual-perceptual processing streams and relay these somewhat separable inputs into the hippocampus (Teyler & DiScenna, 1986). The result may be that a critical role of hippocampus is to bind the separate perceptual and cognitive (e.g. semantic) features of an event in memory. This relatively early theory of hippocampally-based indexing for the featural properties of an experience remains a forerunner of the many theories proposed to explain hippocampal functioning in memory (Teyler & Rudy, 2007). Greater

associative encoding involves the more extensive combination of the disparate yet constituent features of an experience. Under this reasoning, indexing theory would posit that hippocampus activation during the encoding of events that subsequently achieve recollection status should be enhanced according to the contextual quality of the recalled memory, because greater contextual recall indicates that greater associative encoding was achieved. Therefore, item-memories that could have arisen from either an explicitly accessible memory representation for the item alone, or a feeling of familiarity towards it, may be more dependent on extra-hippocampal MTL structures (Davachi et al., 2003). Indeed, previous evidence suggests that, while hippocampus shows discriminatory processing for subsequently recollected experiences (Sneve et al., 2015; Davachi et al., 2003), other MTL structures, namely perirhinal cortex, predicts both subsequent item and source memory. This implies that extra-hippocampal structures may support a foundation of future memory irrespective of the depth or quality of associative encoding, whereas hippocampus engages preferentially under the binding of multi-featural representations in memory (Davachi & Wagner, 2002; Davachi, 2006). Thus, the present evidence is in accordance with this view: bilateral hippocampus demonstrated discriminatory processing for subsequent source memories, as activation was significantly higher relative to both forgotten items and items remembered without source. Therefore, the extent of processing in hippocampus seems related to the subsequent status of a memory after a short-delay, supporting the hypothesised intensity-dependent encoding model for the development of short-duration memories.

If the hippocampus is differentially engaged under short-duration encoding based upon the subsequent memory quality (or strength (Squire, Wixted, & Clark, 2007)) exhibited at test, then this also implies the recruitment of somewhat different neural mechanisms supporting the encoding of short-duration recollection and item memories. However, it is known that visual recognition is an inherent combination of both explicit memory for an event and processes that amount to a feeling of familiarity towards it (Yonelinas, 2001). By extension, this amalgamation of episodic memory processes will naturally have been more evident under conditions of item-only memory observed here, to the extent that item-only memory is more equatable to 'know' judgments in a 'remember-know' paradigm than source memory is. Despite this possible confound, it holds that source-memory recollection, as operationalised in the present study, represented a more explicitly recalled contextual experience, thereby rendering the encoding mechanisms underlying these dissociable subsequent memory types directly amenable to empirical testing against one another. In accordance with this dissociation in recollection and familiarity processes, Carr and

colleagues (2009) found that consistent 'know' judgments were associated with only chance memory performance for episodic details. The current results are thus in support of the claim that somewhat separable neural mechanisms are associated with the encoding of subsequently recollected events and (predominantly) subsequently familiar events (Diana et al., 2007; Yonelinas, 2001). This finding is also in good accordance with previous research highlighting a role for hippocampus in memory *retrieval* that is selective to recollective accounts (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000). Hence, if a critical role of the hippocampus is to index cortical patterns associated with an experience (Teyler & Rudy, 2007), and such patterns become repeatedly indexed throughout the stages of the memory lifecycle, then one would expect this similar discrimination of recollected experiences from familiarity-based ones also at retrieval.

In sum, the results reported here are in support of additional hippocampus processing that was selective to subsequently recollected events only, implying both an intensity-dependent model for true episodic memories that survive a short-duration, and a dissociation in neural encoding signatures leading to familiarity-based and true episodic memories in the hippocampus.

4.2. Cortical findings

The current investigation also provides evidence for a cortical-level intensity-dependent model of activation for memories that survive a short duration, whereby the strongest recruitment in episodic regions under encoding predicted the quality of memory retained across a short delay. In fMRI, activation levels are inferred by oxygenation changes in the blood as an indirect result of neuronal metabolic processes. Activation intensity therefore refers to the magnitude of indirectly measured neuronal-metabolic processes, of which high levels of activity in relation to memory are believed to reflect rapid consolidation processes at the synapse. The notion that such synaptic processes are the neurobiological consequence of memory is not in the least controversial, and such processes are known to initiate within a timeframe of milliseconds and can persist from minutes to hours (Dudai, 2004). A recently activated synapse can also be 'tagged' to undergo subsequent synaptic consolidation (Dudai, 2004; Frey & Morris, 1997). Thus, immediate synaptic consolidation, associated with activity-intensity levels, may be a prerequisite for any memory to first survive representation across a short delay.

Indeed, the present results support this, insofar as greater activity levels were found in a distributed bilateral cortical network for both source memories relative to item-only

memories recalled after a short-delay (T1), and naturally for source memories relative to forgotten representations at T1. This indicates that an intensity-dependent principle applies during the formation of subsequently remembered items at the cortical level also, since the degree of activation in such networks was found to differ between the encoding of recollection and more familiarity-based memories. Cortical clusters identified in the current source memory analysis were found to have very good agreement with episodic-encoding regions revealed by meta-analyses (Kim, 2011). Specifically, additional significant activations were found for source memory encoding in bilateral fusiform gyrus and lateral occipital regions, as well as left superior frontal and inferior frontal cortex (in IFG) (see Figure 5; Appendix H). Left IFG has been documented as expressing a levels-of-processing effect, wherein its activation is responsive to additional semantic encoding at study (Kapur et al., 1994; Otten, 2001), consistent with evidence revealing its role in semantic encoding and the selection of goal-relevant item information for enhanced cortical representation (Blumenfeld & Ranganath, 2007; Xue et al., 2013). In the present study task, participants were required to make a decision based on whether they believed a certain action could be performed on a given object, which also necessitates the recall of semantic world knowledge (although not necessarily for successful memory encoding). It may be, then, that deeper encoding was achieved in trials where there was greater need to verify one's decision with semantic memory, that is, in instances where more deliberation was required, possibly due to moral or physical ambiguity relating to the decision. While this is speculative, the present results do indicate that differential activity in this region and midline prefrontal regions was associated with the formation of stronger memory representations, with stronger activations predicting source recollections but not item-only memories (Figure 5).

Over a short delay, additional processing in perceptual regions involved in the occipito-temporal, or 'ventral' visual pathway was also observed for recollection encoding relative to forgotten items, and between recollection and familiarity-based encoding. Given the ventral pathway's specific role in object discrimination (Cansino et al., 2002; Grill-Spector et al., 2001; Malach et al., 1995), it seems reasonable that greater representation in memory is subserved by additional processing in such task-specific regions (note while no significant clusters were found relating to structures in the occipito-parietal 'dorsal' visual pathway when the sample size was necessarily reduced, the reader is referred to Appendix B, which indicates that the source memory sample may have been underpowered to uncover effects here). Nevertheless, the encoding of subsequently recollected memories was found to involve additional recruitment of perceptually-relevant brain regions. Moreover, as this recollection

encoding was in concert with greater hippocampal recruitment (Figure 6), our findings may also (albeit indirectly) support hippocampal indexing of such task-related cortical activation patterns under encoding. Indeed, previous research indicates that recollection memories are characterised by greater involvement of perceptual regions under encoding (Sneve et al., 2015), and that only recollection memory is characterized by the recapitulation of such perceptual regions during memory *retrieval* (Skinner & Fernandes, 2007). Consistent evidence between cortical activation patterns at encoding and retrieval gives credence to the notion that episodic memory traces maintain a certain stability in terms of the cortical pattern elicited throughout memory lifecycle stages (Teyler & Rudy, 2007). Thus, additional activity in task-perceptual regions was instrumental to the formation of recollection memories that survived a short-delay, Further, greater recruitment was observed during the processing of subsequent recollection traces relative to item-only memory traces, implying that the magnitude of neuronal responses in task-relevant networks was causative in determining whether memory would evolve into a familiarity-based item representation or a more consciously accessible recollective experience at T1.

4.3. Durable Memory Findings

Having established that short-duration representations of episodic memories are in-part the product of stronger recruitment in memory encoding networks, the analysis then focused upon investigating whether additional activity was exhibited under the encoding of durable relative to short-duration episodic memories. Collaborating previous research (Sneve et al., 2015), hippocampus did not show greater neural recruitment under the encoding of durable source recollections relative to short-duration recollections. This speaks against the encoding-intensity principle in the hippocampus, the brain structure almost unanimously believed to be the most crucial for episodic memory development (Teyler & Rudy, 2007). At the cortical level, results found a link between right PPC activation and the encoding of durable recollection memories. Note, however, that the finding of this particular cortical region does not overlap with previous durable memory investigations. Evidence was found for additional activation in both superior (dorsal) and inferior (ventral) PPC in the present study. Activity in dorsal PPC is widely believed to reflect goal-directed attentional processes during a memory task (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008), and is often associated with successful encoding (Uncapher & Wagner, 2009). In contrast, ventral PPC activity is most associated with the capture of reflexive attention, and most often accompanies encoding failure as a consequence (Corbetta & Shulman, 2002; Uncapher & Wagner, 2009). Thus,

while posterior parietal activations *are* often seen in studies of memory, the well-established role of these regions in top-down and bottom-up attention has led to conclusions stating that their activation during memory tasks reflects attentional processes during encoding and retrieval (Cabeza et al., 2008). In strong support of this, results from patient studies indicate that PPC lesions do not tend to cause episodic memory deficits (Cabeza et al., 2008; Hutchinson, Uncapher, & Wagner, 2009), and a study employing temporary neuromodulatory interference by transcranial magnetic stimulation did not find a causal link between PPC disruption and episodic encoding (Rossi et al., 2006). In addition, recent research using the same task does not support a role for the PPC in the encoding of durable episodic memories (Sneve et al., 2015), and no previous research has found evidence for PPC activation during durable memory encoding (Liu et al., 2013; Uncapher & Rugg, 2005). Thus, while it is possible that the PPC activation under durable memory encoding seen here may have been linked to differences in attentional processing, inconsistent results from lesion data (patient and temporary) and previous durable memory research suggests that caution may be warranted towards this interpretation. Specifically, this interpretation is made somewhat problematic by the relatively low number of T2 source memory trials going into the time-wise comparison, increasing the chance of sampling error for mean BOLD activations at the individual level. As such, future research could shed light on the possible role of attentional processing regions in the PPC during the encoding of both durable and truly episodic memories.

Previous investigations supporting the encoding-intensity account in durable memory encoding have all found additional activation in cortical regions well-established as involved in memory encoding (Carr et al., 2010; Kim, 2011; Liu et al., 2013; Uncapher & Rugg, 2005). In contrast, present results were otherwise found to have rather high consistency with recent research unsupporting this intensity account (Sneve et al., 2015), as no additional hippocampus or cortical activation in accepted episodic memory-relevant structures was found during durable memory encoding (no trends either; see Appendix E). This implies that the most durable memories may not be a product of greater neural recruitment (believed to reflect immediate consolidation) under encoding. Instead, results seem more in line with the notion that a critical activity threshold is first required to be reached for experiences to persist in memory at all (Dudai, 2004). Beyond this, however, our results provide (indirect) support for the role of alternative mechanisms in determining the selection of memories to undergo post-encoding consolidation. It follows, then, that either post-encoding consolidation itself, or brain mechanisms under encoding that are unrelated to the level of neural activation (e.g.

enhanced connectivity) should be more causative in determining the selection of potentially durable memories. Indeed, enhanced functional coupling of episodic structures under encoding seems to be instrumental towards durable memory formation (Ritchey et al., 2008; Sneve et al., 2015), possibly reflecting a 'salience tagging' of memories to undergo further processing (Stickgold & Walker, 2013). Hence, future research into different types of durable memory may find fMRI connectivity measures to be an enlightening approach in exploring the interaction between a waking experience and its subsequent stabilization as, or integration into, a memory network.

Given that the prolonged delay between encoding and test involved many nights of sleep, it is possible that sleep-dependent selection mechanisms (Stickgold & Walker, 2013) are preferentially engaged for the experiences that *are* most strongly encoded, but the threshold level for this may be equivalent to that which is needed for representation across a short delay. This threshold may also be the equivalent of that required for the 'tagging-and-capturing' of synapses to undergo long-term potentiation, whereby initially unstable and weak memories are singled out at the neurobiological level to undergo later stabilisation through consolidation (Frey & Morris, 1997; Rogerson et al., 2014). Thus, the present fMRI study may corroborate neurobiological models that pose that the threshold required for future systems consolidation may be equivalent to that required for initial memory representation. By extension, only experiences that are initially successfully consolidated (and consequently endure a short-delay) may become susceptible to future offline systems consolidation processes in the brain.

4.4. Relation to Previous Durable Memory Research

The present results may be at odds with previous research into memory durability for a number of reasons. First, it may be that hippocampal and perirhinal activity are predictive of future memory durability provided that the memory has been previously reactivated as part of a test-retest procedure (Carr et al., 2010). Although Carr and colleagues attempted to reduce this confound, it is unclear to what degree it may have contributed to results, given the established memory advantage conferred by retested material (Liu et al., 2013). Further, under the 'tag-and-capture' hypothesis, threshold levels of induction create the potential for long-lasting changes in synaptic plasticity. However, neural activity subsequent to such tagging is also vital in determining lasting memory representations through the subsequent 'capture' of synthesized proteins by reactivated neuronal networks (Redondo & Morris, 2011). As such, it remains an intriguing possibility open to future research as to whether the

effect observed by Carr and colleagues was related to the intentional encoding paradigm used, or due to the additional reactivation of memories at a short-delay test, potentially related to a synaptic-tag-and-capture advantage.

It may also be that the validity of the previous paradigms used in addressing true episodic memory is questionable, due to the reliance upon participant measures of confidence as a means of dividing familiarity from recollection (Skinner & Fernandes, 2007). While such measures are not without their merit, arguably, both 'remember' and high-confidence-scaled responses would present with a larger confound of intermixed familiarity memories than would be evident under a procedure that actively tests for the recollection properties of the memory, such as in the present experiment. In addition, most previous durable memory fMRI investigations used words as experimental stimuli. Hippocampal activations have been more consistently shown during pictorial encoding than during the encoding of words, and this lack of consistency for words has been attributed to familiarity properties conferred by words. Indeed, it has previously been proposed that the human encoding system has evolved to preferentially encode novel events, since these were (and still are) likely to confer the highest survival value throughout our evolution (Tulving, Markowitsch, Craik, Habib, & Houle, 1996). Hippocampal involvement may therefore be somewhat dependent on the novelty status of encoding stimuli. Therefore, an encoding paradigm employing pictorials (which by virtue of sheer variation in appearance are more novel) is arguably more optimal if one's goal is to delineate true episodic memory signatures in the brain. Moreover, a lack of clear-cut hippocampal findings for transiently remembered words (Liu et al., 2013) supports the notion that remembering may have been more familiarity-driven in some previous durable memory investigations.

To investigate this, the present study concatenated item and source memories into one memory condition (naturally composed of a mixture of recollection and familiarity memories), under the rationale that similar results should be observed as to those seen in previous durable memory investigations if these reflected more familiarity-based, or intermixed recognition memory processes. Of course, this did not make possible the disentangling of memories for which one retained an explicit representation from those based upon weaker representations, but rather investigated memory for stimuli irrespective of strength. Importantly, this new analysis conferred a concurrent boost in experimental power, due to the higher number of T2 memory observations, and a larger sample as a consequence of this. Firstly, a highly similar cortical network was revealed for the encoding of memories that endured a short-delay relative to forgotten items, including bilateral perceptually-relevant

regions and default-regions, as well as left lateralized prefrontal regions (Figure 9), in very good agreement with meta-data (Kim, 2011).

Crucially, a time-wise contrast for short-delay and long-delay recognition memory performance revealed additional, novel evidence against the encoding intensity hypothesis. Namely, the durability of *recognition memory* also does not seem to be supported by greater activations in episodic networks under encoding. Since no significant clusters survived, this second analysis somewhat supported the results of the first: no additional cortical activity was evident between short-duration and long-duration memory in established episodic structures, irrespective of subsequent memory strength. However, it should be noted that prior to correction for multiple comparisons, a trend was observed towards greater deactivation in the PCC (a similar region identified by Liu et al., (2013) as activated) in the present data (see Appendix F), possibly hinting that greater statistical power could uncover effects here. Nevertheless, this novel finding also suggests that the selection of memories to undergo systems consolidation is not determined by greater activations in memory networks beyond a prerequisite threshold for short-delay representation, *regardless of the quality of the subsequent memory*. Follow-up interaction analyses supported this interpretation, insofar as no cortical regions were evident where BOLD activity related differently to recognition memory performance according to the encoding of short-duration or durable memories.

As it stands, then, the reasons for the conflicting results between the current paradigm (present study; Sneve et al., 2015) and previous paradigms remain unclear. However, the present study provides evidence that the original confound in the literature (that inspired the present within-groups experiment) cannot necessarily be attributed to the between-subjects paradigm used by Sneve and colleagues. It is suggested that inconsistent results may be a result of varying paradigms, particularly in terms of stimuli type (words/pictorials), or test-retest procedures that possibly confer synaptic-level advantages for memory representations to become durable once reactivated (Carr et al., 2010; Redondo & Morris, 2011). It may also be that the activation intensity exhibited under the encoding of stimuli remembered following a delay of <=1 week is predictive of memory durability, as has previously been found (Carr et al., 2010; Liu et al., 2013; Uncapher & Rugg, 2005), whereas for memories to remain stable over several weeks, entirely different processes are at play. Future research is needed to investigate and reconcile such discrepancies.

4.5. Memory Breakdown

Intriguingly, despite an extra ~3 weeks between encoding and test adopted in a former experiment (Sneve et al., 2015), participant performance was significantly worse in the present experiment in the long-delay domain for both recollection and familiarity-based memory. The crucial difference between the current sample and the previous was a difference of 100 items shown at encoding, and the administration of a short-delay test prior to the long-delay test in the scanner environment. Hence, the detriment observed for T2 memory performance was caused by either 1) a selective interference effect upon post-encoding consolidation processes, or 2) a faster decay of successfully encoded hippocampally-grounded recollections, and was a product of (a) encoding twice as many stimuli, (b) the additional administration of a short-delay memory test, or (c) a combination of both.

Further fMRI analyses revealed that average encoding activity in the brain was significantly reduced in distributed networks under later-viewed encoding stimuli than under the first (Figure 12). However, the temporal presentation order of encoding runs (1-4; see Figure 1A) had no effect on subject recollection performance after either a short (T1) or long (T2) delay. Thus, since recollection memory behavioural effects were not observed in concert, it is believed that the fMRI effects observed were most likely attributable to neuronal habituation to repetitive sensory stimuli (Singh, Kim, & Kim, 2003), rather than related to memory performance.

Recent compelling evidence suggests that the manner in which we forget may be dependent upon the memory type, as underpinned by dissociable neural processes (Sadeh, Ozubko, Winocur, & Moscovitch, 2014). Evidence suggests that, while the neocortex makes use of overlapping neural representations for similar stimuli, the hippocampus is able to assign unique and separable representations to comparable stimuli, a feat known as ‘pattern separation’. This pattern separation may be made possible because a critical function of the hippocampus is to bind the composite features of an experience (i.e. spatiotemporal context) in a memory representation, which may in turn enable one to distinguish between similar but separate recollection memories. Crucially, recollection memories may be more susceptible to decay through ongoing hippocampal-subfield neurogenesis, causing remodeling of hippocampal circuits gradually over time in a manner that isn’t dependent on new experiences (Hardt, Nader, & Nadel, 2013; Sadeh et al., 2014). This decay-like process is believed to occur predominantly during sleep. In contrast, cortical networks display similar activity patterns for similar experiences based on Hebbian learning principles, and hence extra-hippocampal-dependent familiarity memory may be more susceptible to interference by

new experiences. The present results are in line with some of these predictions, as recollection memory was severely reduced at T2 (where a higher criterion and so reduced guessing was observed), possibly indicating that fast decay of hippocampally-grounded recollections was apparent in the weeks between incidental encoding and long-delay test.

Similarly, recent animal research suggests that the rate of adult hippocampal neurogenesis regulates learning and forgetting; increasing hippocampal neurogenesis leads to improved memory encoding via enhanced pattern separation in the short-term (Akers et al., 2014; Sahay et al., 2011), yet the increased demand for network remodeling in order to integrate newly formed neurons may destabilize existing memory networks, and thus promote accelerated forgetting and poorer durable memory. Indeed, increasing neurogenesis rate has previously been shown to accelerate forgetting rate in mice, and thus attenuate durable memory (Akers et al., 2014). Behavioural results in the present study provide support for a relationship between higher memory encoding ability after a short delay and a greater percentage drop-off for durable memory retention ability (see Figure 8): subjects with high recollection at T1 showed a greater fall in T2 recollection memory compared to low performers at T1. Tentatively, it is suggested that this may also be consistent with a theory of decay for hippocampally-based recollection memories (Hardt et al., 2013; Sadeh et al., 2014): the increased pattern separation (thus hippocampal neurogenesis; Sahay et al., 2011) necessary for superior short-delay recollection performance may have accelerated the forgetting rate for durable recollection memories, such that initial high performers experienced faster decay than low performers within the same timeframe, possibly in-part due to higher rates of ongoing neurogenesis in hippocampus.

4.6. Limitations

The separation of true episodic memories from familiarity-based ones was optimised at test using a three-step procedure. This explicit testing for recollection details gives confidence that memory observations falling within this category were a result of true episodic recollection. However, an inherent limitation with a within-subject experiment is the risk that revealing the first surprise memory test enhances the expectation of the second, and therefore introduces a potential confound of self-rehearsal by the second. Nevertheless, the long time delay between first and second test, in addition to the fact that each timepoint tested memory for different items, suggests that the risk of conscious rehearsal strategies was likely minimal. In addition, although a total of 25 participants were scanned during the entire procedure (encoding + 2×test), many had to be excluded due to either excessive in-scanner

movement or an extremely low number of recollection memories at the second test. Consequently, data became rather underpowered to detect fMRI effects for durable recollection memories (see Appendix A & B). Further, low experimental power as a result of small sample size makes it difficult to make inferences relating to null effects, on which the current hypotheses were based. Therefore, the null-effects reported here do not directly argue that no differences in brain activation are apparent between long-duration and short-duration memory formation. Rather, they provide support against the encoding-intensity hypothesis during durable memory formation, and somewhat collaborate previous research carried out on a more highly powered sample (Sneve et al., 2015).

It should also be noted that memory was tested for different items at T1 and T2. Therefore, beta estimates of source memory BOLD activity at T1 will naturally have been partly based upon items in which a durable memory representation would also have been established had they been tested at T2 instead. However, given that subjects only remembered on average ~8% of items with source memory at T2, there is no reason to believe that the number of potential T2 source memories for items tested at T1 would be different from this ~8% average. Therefore, because the number of T1 source memory observations greatly exceeded the number at T2 ($p < 10^{-13}$), a contrast between T1 and T2 source memory would likely contain only ~8% potential T2 source memories being inputted into the model as T1 source memories. Consequently, systematic differences in encoding activity between T1 and T2 would likely have remained sensitive to the statistical tests employed (see Sneve et al., 2015).

5. Conclusion

In conclusion, results indicate that an intensity-dependent principle applies during the formation of memories that survive a short duration, whereby the greatest neural recruitment in hippocampus and cortical episodic-encoding networks predicts the encoding of subsequently recollected memories, relative to those that become subsequently forgotten or remembered by weaker, more familiarity-dependent representations. Thus, the level of engagement of neural networks under encoding determines the short-term retention potential for memories and their subsequent qualities. However, no differences in brain activation were evident between the encoding of subsequently durable memories relative to those subsequently recalled after a short-delay in structures typically thought be involved in memory encoding networks; the strongest activations in memory-related structures under encoding did not predict the most durable memories. This held for both subsequent episodic

recollection (where only weak effects were observed in attention-related structures) *and* subsequent recognition memory; a novel finding. Thus, the results suggest that a critical encoding intensity must indeed first be surpassed if a memory is to potentially withstand the test of time, but that this threshold seems to also be that which is required for a memory to achieve short-duration representation. Hence, the selection of durable memories from this pool of potential candidates crossing the intensity threshold may be primarily determined by offline post-encoding consolidation processes, although potentially aided by alternate neural mechanisms under encoding that do not reflect the level of engagement of neural networks.

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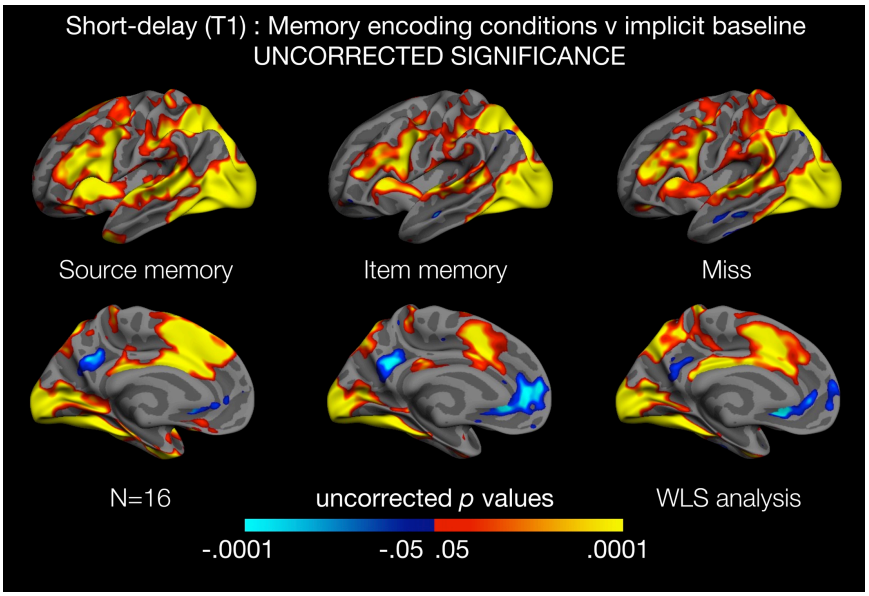
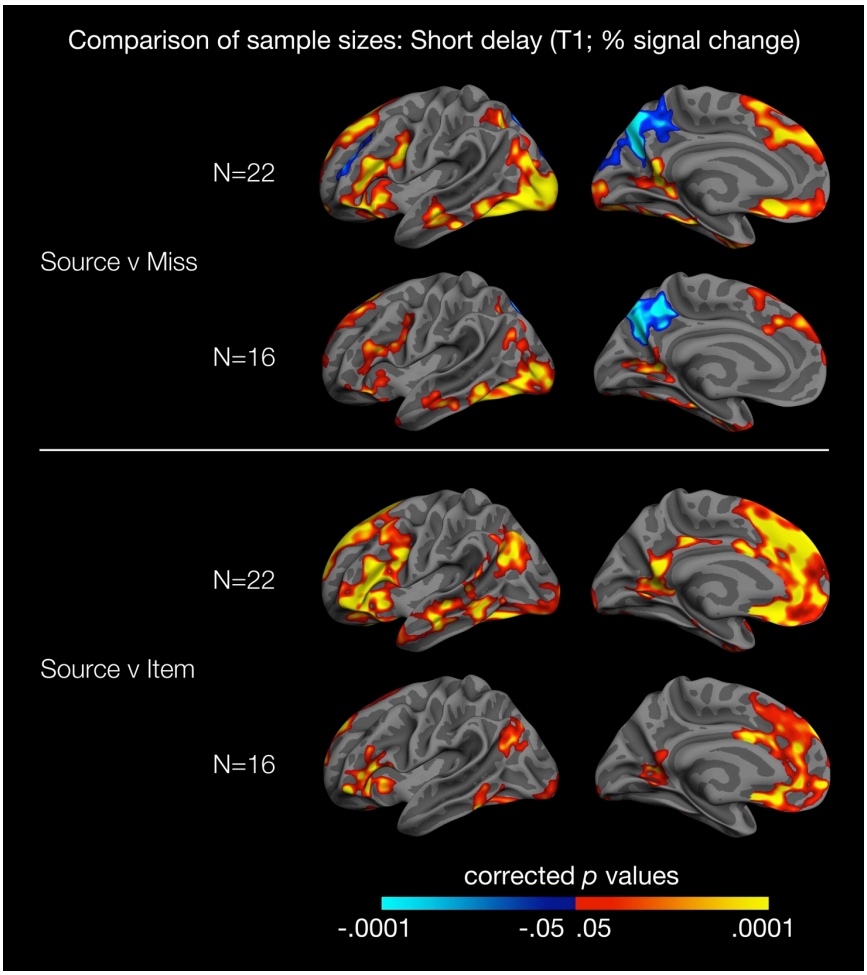
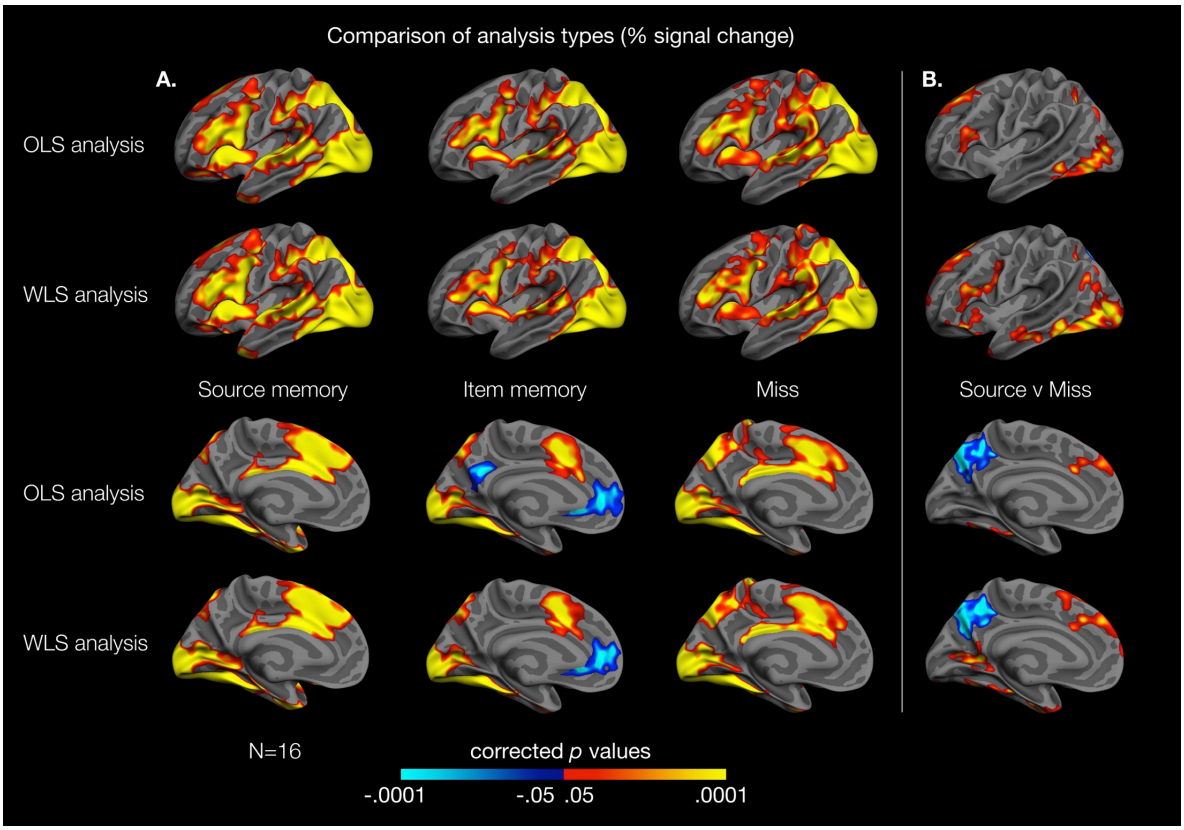
Appendix



Appendix A. Uncorrected significance maps for *memory condition v implicit baseline* contrasts in the left hemisphere only (for illustration purposes). Note that there were trends towards deactivation in typical default-network structures, including precuneus and middle prefronal cortex for all memory condiitons, suggesting that such clusters did not survive correction for multiple comparisons, and that greater experimental power may have uncovered effects here in all subsequent memory conditions

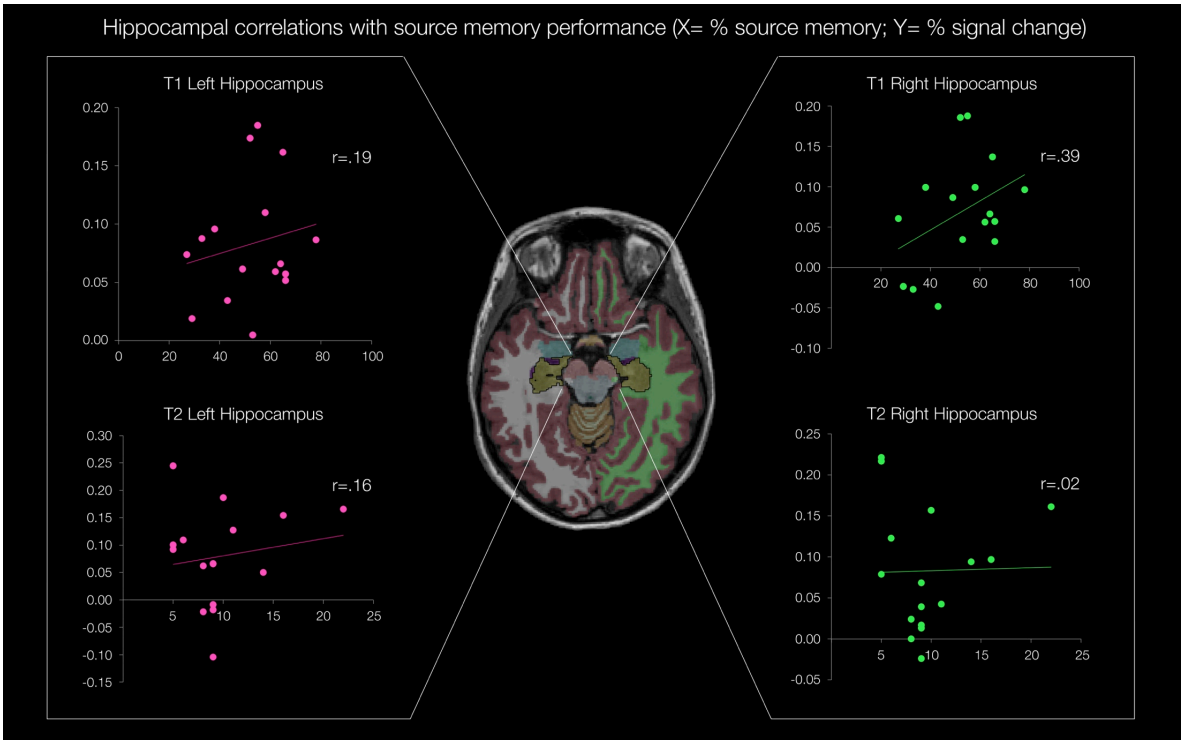


Appendix B: The relative statistical power gained by larger samples in event-related fMRI. llustrates the difference in BOLD activations that the GLM model estimates for 16 and 22 subjects. In general, there was very high agreement between cortical regions identifed for all contrasts across sample sizes, although a greater number of activations in the smaller sample did not survive cluster-wise correction methods for multiple comparisons. As such, activations become far more robust in larger samples.

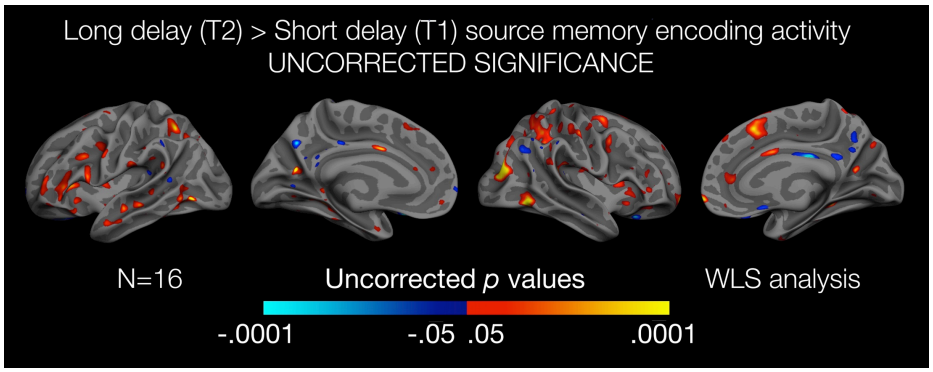


Appendix C (above): As a means of detecting the influence of analysis type upon the BOLD activation results observed, estimated beta-values were submitted to an ordinary least squares (OLS) approach that gives equal influence to subjects with greater variation in BOLD response in the fitting of the GLM model. The figure displays a visual comparison of analysis types. Note that, while there was extremely high agreement between analysis types, output from the WLS analysis appears slightly more constrained against baseline (A.), and appears to yield more robust activations in the pair-wise contrasts (B.). Indeed, since the original voxel data from each subject becomes ultimately averaged to a single number across specified conditions, this assumes that the variance in voxel activation within a subject is negligible. As such, because smaller sample sizes and fewer observations will yield greater variance around the true mean, the WLS approach is likely to prove more robust for the present experiment, particularly due to the lack of source memory observations at T2 (see Figure 3). Consequently, a WLS approach was applied and used to visualize all fMRI results.

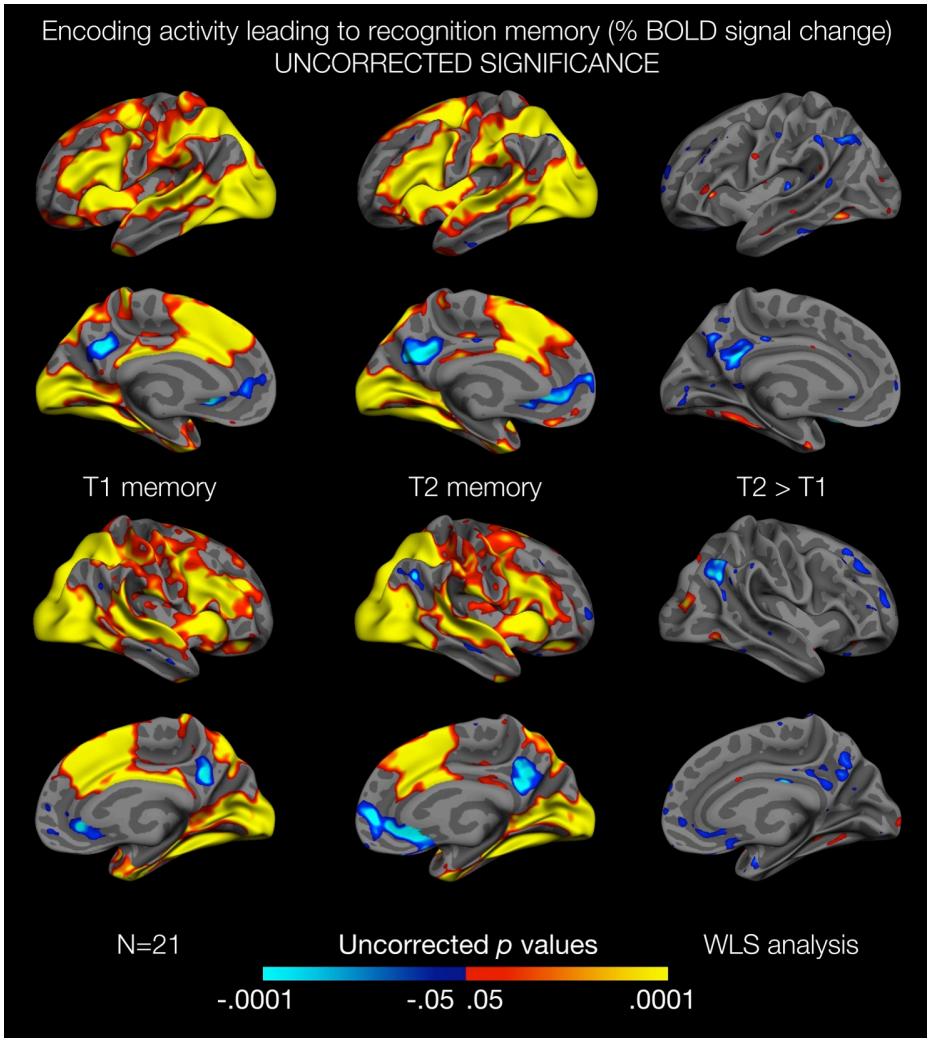
Appendix D (below): Correlations were plotted for left and right hippocampal *source memory v baseline* BOLD values against source memory performance at T1 and T2 (Appendix C). All correlations proved non-significant.

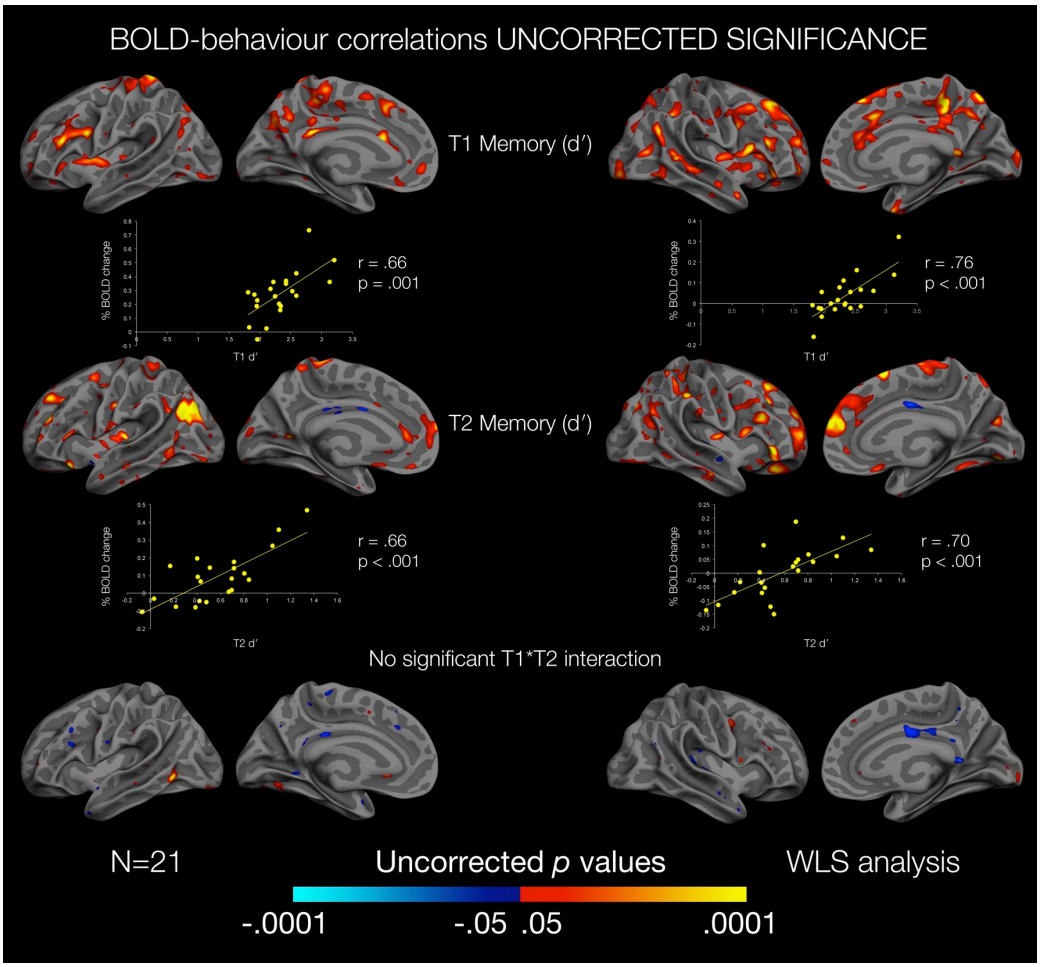


Appendix E. Uncorrected significance maps for a time-wise *T2 source memory > T1 source memory* contrast.



Appendix F (below)*:* Uncorrected significance maps for *T1 recognition memory v baseline, T2 recognition memory v baseline,* and a time-wise *T2 recognition >T1 recognition* contrast. Note that trends were observed towards deactivation in typical default-network areas in posterior cingulate cortex and right supramarginal gyrus in the time-wise contrast.





Appendix G: Uncorrected significance maps for BOLD-behaviour correlations of T1 and T2 recognition memory performance (*d*-prime). Note that no trends were for an interaction between T1 and T2 recognition memory and BOLD correlations.

Appendix H

Cluster Summary: T1 Source Memory

Contrast	Hemisphere	Max *p* (log 10)	X	Y	Z	Mean Cluster *p* (log10)	Region (peak)
Source > base	LH	11.298	-40.1	-42.4	-21.7	0.0002	fusiform
		6.462	-7.8	21.8	48.7	0.0002	superiorfrontal
	RH	9.339	32.7	-85.7	-0.4	0.0002	lateraloccipital
		6.871	9.4	0.5	40.1	0.0002	posteriorcingulate
Item > base	LH	10.405	-42.4	-61.1	-19.6	0.0002	fusiform
		6.141	-42.1	1.7	26.2	0.0002	precentral
		4.751	-51.1	-46.3	10.2	0.0002	bankssts
		4.662	-11.2	10.6	41.7	0.0002	superiorfrontal
		4.31	-30.4	10.8	10.9	0.03371	insula
		-3.802	-4.1	28.6	-2.4	0.00479	rostralanteriorcingulate
	RH	9.801	44.5	-54.1	-11	0.0002	inferiortemporal
		5.134	49.2	-25.9	-2.2	0.0002	superiortemporal
		5.129	9.2	9.8	36.2	0.0002	caudalanteriorcingulate
		4.711	40.7	3.5	25.6	0.0002	precentral
		-4.502	10.3	50.9	-5.6	0.0006	medialorbitofrontal
Miss > base	LH	10.367	-36.2	-82.7	-14.9	0.0002	lateraloccipital
		6.825	-37.7	12.5	10.8	0.0002	parsopercularis
		5.718	-7.4	-23.2	31	0.0002	posteriorcingulate
	RH	9.592	45.5	-53.2	-11.9	0.0002	inferiortemporal
		6.594	36.6	4.1	26.2	0.0002	precentral
		6.018	11.3	13.3	42.5	0.0002	superiorfrontal
Source > miss	LH	-5.773	-8.9	-68.6	34.2	0.0002	precuneus
		4.937	-28.7	-84.3	4.5	0.0002	lateraloccipital
		4.275	-10.8	26	54.7	0.0002	superiorfrontal
		3.519	-16	-53.9	7.2	0.0026	isthmuscingulate
		3.338	-47.8	2.5	25.8	0.0002	precentral
		3.186	-57.9	-21.5	-20.6	0.02563	middletemporal
		3.182	-42.5	26.8	-13.5	0.003	lateralorbitofrontal
	RH	-5.516	58	-37	38.1	0.0002	supramarginal
		4.242	30.9	-84.5	0.9	0.0002	lateraloccipital
		-3.458	10.2	-73.4	48	0.0002	superiorparietal
Source > item	LH	5.183	-34.2	32.9	-1.7	0.0002	parstriangularis
		4.94	-8.4	52.8	36.1	0.0002	superiorfrontal
		4.228	-55.1	-44.9	-21.3	0.0002	inferiortemporal
		3.166	-19.5	-56.9	8	0.02761	precuneus
		2.96	-42	-68.1	27	0.002	inferiorparietal
		2.776	-25	-91	-13.7	0.01435	lateraloccipital
	RH	6.516	9.4	40.3	3.8	0.0002	rostralanteriorcingulate
		4.337	40.5	-54.7	-15.1	0.01157	fusiform
		3.998	52.9	22.1	9.8	0.0002	parstriangularis
Item > miss	LH	-3.36	-12.1	-54.9	28.8	0.0002	precuneus
		-2.998	-11.1	38.7	11	0.02524	rostralanteriorcingulate
	RH	-4.054	54.3	-52.1	37	0.0002	inferiorparietal
		-3.99	11.2	39.9	2.8	0.00858	rostralanteriorcingulate
		-3.026	6.4	-9.2	30.8	0.0012	posteriorcingulate
		-3.004	7.3	-63.2	57.7	0.02227	precuneus

Appendix I

Cluster Summary: T2 >T1 Source Memory

Contrast	Hemisphere	Max *p* (log 10)	X	Y	Z	Mean Cluster *p* (log10)	Region (peak)
T2 > T1	LH	-	-	-	-	-	-
	RH	-4.101	39.2	-81.6	20.2	0.0001	inferiorparietal
		-2.428	31.6	-48.1	48.2	0.013	superiorparietal

Appendix J

Cluster Summary: Recognition Memory

Contrast	Hemisphere	Max *p* (log 10)	X	Y	Z	Mean Cluster *p* (log10)	Region (peak)
Recognition v base	LH	12,991	-39,8	-42,8	-22	0,0002	fusiform
	RH	12,111	42,7	-68,1	-14,4	0,0002	fusiform
Recognition v miss	LH	6,479	-37,5	-43,3	-22,1	0,0002	fusiform
		4,634	-41,3	38,2	-13,2	0,04391	parsorbitalis
		-4,029	-8,7	-72,1	39,8	0,0002	precuneus
		3,51	-20,6	26,9	47,9	0,0002	superiorfrontal
		3,39	-46,8	2,4	25,9	0,0004	precentral
	RH	-6,172	57,7	-37,4	38,1	0,003	supramarginal
		-4,858	8,8	-73,3	47,6	0,0002	superiorparietal
		4,363	46	-77,7	1,3	0,0002	lateraloccipital
T2 > T1	LH	-	-	-	-	-	-
	RH	-	-	-	-	-	-